Exercise intervention may play a potential therapeutic role in patients with glioblastoma multiforme (Review)

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Abstract. The present study conducted an extensive review of the literature that describes the molecular pathogenesis of cancer and glioblastoma multiforme (GBM), exploring physiological adaptation resulting from exercise training in the broader context of cancer and brain tumors, with a specific emphasis on GBM, aiming to discern the implications of exercise in improving the quality of life (QoL) of affecting patients. GBM is the predominant aggressive malignant primary brain tumor with a high mortality rate. GBM involves multiple pathways that can be targeted by exercise training. Exercise has shown its value in various other cancer types and offers a promising approach for GBM. Exercise training is regarded as a safe and feasible adjunctive treatment to improve the QoL of patients with brain tumors, including GBM. Nevertheless, further research is required in order to fully elucidate the mechanisms through which exercise affects cellular processes impacted by cancer and its treatments, with a specific focus on GBM. While exercise training guidelines have been established for cancer patients in general, there is currently a lack of specific guidelines tailored to patients with GBM. Clear guidelines are essential to assist clinicians in determining the most appropriate exercise type, intensity and frequency for patients to optimize their rehabilitation process.

Contents

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1. Introduction

Brain and other central nervous system tumors are the leading causes of mortality due to cancer among females aged <20 years and males aged <40 years (1). Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor affecting adults, comprising 16% of all primary brain tumors and 54% of all gliomas (2). GBM is the most aggressive diffuse glioma of astrocytic origin and is classified as a grade IV glioma based on the World Health Organization (WHO) classification (3). GBM is extremely lethal, being associated a 5-year survival rate of 5% and a median survival rate of 16 months following diagnosis (4). GBM is classified into primary and secondary subtypes, which develop through different genetic pathways (5). Primary GBM comprises ~90% of cases diagnosed, which arise *de novo,* without evidence of a precursor tumor, and most commonly occurs among older patients (6). Secondary GBM arises from low-grade diffuse astrocytoma or anaplastic astrocytoma and most commonly occurs in younger patients (6). In 2021, the WHO reclassified diffuse glioma based on the isocitrate dehydrogenase (IDH) mutation status, categorizing it into IDH wild-type glioblastoma and IDH-mutant glioblastoma (7). In addition to the high mortality rate, patients with GBM are characterized by a low health-related quality of life (QoL) compared with patients with other types of (8).

Treatments for GBM are typically aggressive, utilizing a combination of surgery resection, radiotherapy and chemotherapy (9). Recent advancements in the treatment of GBM, including targeted therapy (e.g., monoclonal antibodies) and immunotherapy [programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune-checkpoint inhibitors] offer new hope for patients; however; further research is required in order to fully understand and optimize these approaches to improve the outcomes of patients (10). Regrettably, standard GBM treatment is associated with a wide range of side-effects and secondary morbidity. Both tumor burden and treatment may result in cognitive impairment, psychological distress, poor coordination and motor control,

and impairments in physical functioning, fatigue, myopathy and neuropathy (11). These side-effects impair the activities of daily living and compromise the QoL of patients with GBM.

Due to toxicities from treatment and the high mortality rate associated with GBM, there is a need for new interventions to improve the QoL and reduce the mortality rates of patients. Among the strategies being pursued, exercise has emerged as an intervention that warrants further investigation. Exercise has the potential for the direct and indirect prevention of both cancer and comorbid diseases (12). Pre-clinical and clinical studies have also shown that physical activity and structured exercise improve the efficacy of cancer treatments as well as prognosis (13,14). In addition, a previous meta-analysis of randomized controlled trials revealed that exercise during and after treatment in patients with cancer improved physical and psychological parameters, and the QoL (15).

The present review briefly discusses the genetic pathogenesis of GBM. The findings of currently available literature on physiological adaptation from exercise training in GBM are summarized and the mechanisms through which exercise can improve the QoL and reduce the mortality rates of patients with GBM are also discussed. The present review also summarizes the underlying mechanisms through which exercise may enhance the efficacy of treatment, improve overall health and lower recurrence rates in cancer populations. Finally, the updated exercise training guidelines for patients with cancer are also discussed.

2. Literature search strategy

A literature search was carried out using the MEDLINE/PubMed of the National Library of Medicine, Scopus and Google Scholar databases to identify relevant articles. The search methodology used a combination of the following key words: 'cancer', 'brain tumor', 'glioma', 'glioblastoma', 'physical capacity', 'exercise', 'training' and 'rehabilitation'. A search of the reference lists of case studies and the clinical trials included in the present review was also performed for the potential to detect other relevant studies.

3. Genetic and molecular pathogenesis of GBM

Over the past two decades, multiple molecular variations have been identified in GBM, which have allowed for a more comprehensive description of GBM, as well as an understanding of the glioma landscape and pathways disrupted in this type of cancer. The primary and secondary GBM subtypes appear to develop through different genetic pathways and likely differ in prognosis and response to therapy (5,6). Primary GBM typically exhibits the overexpression of the epidermal growth factor receptor (EGFR) gene, the loss of heterozygosity (LOH) of chromosome 10q, which encodes phosphatase and tensin homolog (PTEN), TERT promoter mutation, CDKN2A (p16) deletion, and less frequently, mouse double minute 2 (MDM2) amplification (5,6,16). The mutations of secondary GBMs include the LOH of chromosome 19q, the amplification of platelet-derived growth factor (PDGF)A and PDGF receptor-α (PDGFR-α), retinoblastoma (RB), and mutations in IDH1/2, p53 and alpha-thalassemia/mental retardation, X-linked (16). These genetic mutations result from the dysfunction of three main signaling pathways: The receptor tyrosine kinase (RTK)/RAS/phosphatidylinositol 3-kinase (PI3K) pathway, p53 pathway and RB signaling pathway (17). Other pathways implicated include hypoxia-inducible factor (HIF), AMP-activated protein kinase (AMPK) activity, anaerobic bioenergetics and inflammatory responses in the brain (16-19). Studies have also shown that epigenetic mechanisms, such as promoter CpG island DNA hypermethylation, the aberrant expression of microRNAs (miRNAs/miRs), and the post-translational modification of histone protein also play a role in the development and progression of GBM (20).

The RTK singling pathway is well-recognized as one of the most common genetic alterations in malignant gliomas (17). The EGFR and PDGFRA genes are the most recurrently mutated and amplified (17). EGFR downstream signaling pathways control a wide range of cellular activities, including growth, migration and survival. This pathway further promotes cell division, tumor invasiveness and resistance to chemotherapy in GBM (21). EGFR activity is enhanced by amplifying EGFR protein expression, deleting downstream pathway inhibitors, and constitutively active EGFR (EGFRvIII), which is the most common mutation among EGFRs amplified in GBM (17). This subsequently leads to the activation of numerous downstream signaling pathways, such as the PI3K/Akt/rapamycin-sensitive mTOR-complex (mTOR) pathway (22). Understanding the complex pathways associated with the growth and progression of GBM will enhance novel treatment options, such as targeted therapy via monoclonal antibody administration.

HIFs and other metabolites play a critical functional role in the tumor microenvironment (TME), which includes cancer-associated fibroblasts, endothelial cells and immune cells, and serves to foster a microenvironment structure for tumor growth and proliferation (23). HIFs act to promote angiogenesis, increasing the blood and nutrient supply to cancer cells. The angiogenic switch found during cancer progression is associated with exponential cancer progression through HIF-1, activating an increase in vascular endothelial growth factor (VEGF) expression (23). Previous research has demonstrated an increase in VEGF expression in the TME, which supports the tumor metabolically, further ingraining itself into the tissue and eventually allowing intravasation into the systemic circulation and metastasis (24). The previous study by Cao *et al* (24) demonstrated that the amplification of 14-3-3zeta (pro-apoptotic) gene activated the PI3K/Akt pathway associated with the overexpression of HIF-1a and VEGF in glioma. It is through this mechanism that malignancy increases and prognosis decreases with GBM diagnosis.

AMPK is an essential mediator in maintaining cellular energy homeostasis and plays an essential role in regulating growth, metabolism, autophagy and cell polarity in healthy cells (25). For this reason, the regulation of AMPK and its shift to promote tumor development in cancer must be understood. A previous study demonstrated that the high expression of AMPK plays a critical role in bioenergetics pathways in GBM through interaction with the HIF-VEGF pathway, aiding in tumor growth (26). AMPK also mediates glucose transporter protein expression on the tumor cell, allowing for increased glucose uptake for bioenergetic pathways and ATP production at the tumor (26). Cyclic AMP responsive element-binding protein 1 (CREB1) is implicated as the primary factor that

promotes this AMPK link to HIF and glucose transporter protein activity (26). Previous research has explored the role that these three factors play and the mechanisms through which this pathway may be altered to combat this effect. It appears that the inhibition of CREB1 and AMPK leads to a reduction in glucose transporter protein and HIF expression, and a reduction in the expression of GA-binding protein alpha chain, a transcription factor responsible for the control of mitochondrial function (26).

By-products of energy pathways are implicated in the progression of GBM. The metabolic shift of cancer cells into a glycolytic state leads to an increase in lactate production (27). Lactate production and the associated receptor hydroxycarboxylic acid receptor 1 (HCAR1) are the primary factors that promote tumor growth and progression (28). The TME cultivates anaerobic pathways of energy production and therefore promotes substantial lactate accumulation and upregulation of HCAR1 receptors (28). This upregulation is associated with angiogenic signaling and VEGF overexpression, specifically in the cerebral environment, which is highly unique to GBM, as, to the best of our knowledge, there is no evidence in the current literature that this receptor activity is upregulated in the periphery in those diagnosed with GBM (28). Aldehyde dehydrogenase (ALDH) is another glycolytic metabolite that is implicated in the metabolic dysfunction of GBM. It has been shown that ALDH increases the malignancy of GBM through the upregulation of its expression (29). This association with an increased malignancy is due to the promotion of glioma stem cells (GSCs), which increases the aggressiveness of GBM cells (29). GSCs are resistant to temozolomide, allowing them to survive therapy, leading to disease recurrence (30). In addition, these cells overexpress VEGF receptor 2 (VEGFR2) increasing endothelial cell proliferation, migration, and blood vessel permeability leading to increased edema in GBM (30). Recent literature shows the selective deletion of stromal cell-derived factor 1, which signals through CXCR4 expression on GSCs, inhibits tumor growth and prolongs survival in GBM, suggesting that targeting GSCs may inhibit tumor growth and limit resistance to current anti-angiogenic therapies (31).

p53, as a tumor suppressor and transcription factor, plays a crucial role in preventing tumor development by inducing the apoptosis of damaged cells, maintaining genomic stability, inhibiting angiogenesis and regulating cell metabolism and the TME (32). p53 is also a key regulator of cellular metabolism, stemness, autophagy, invasion, metastasis, the TME and immunity (33). In GBM, the p53 pathway is frequently deregulated, with research demonstrating alterations in the ARF-MDM2-p53 pathway in 84% of GBM cases according to The Cancer Genome Atlas (2013) and up to 94.1% of GBM cell lines (34). In secondary GBM, p53 mutations may occur alongside IDH1 mutations, contributing to the complexity and controversy in p53 research in GBM (35). PTEN a tumor suppressor is a negative regulator of a major cell growth and survival signaling pathway, namely the PI3K/Akt signaling pathway (36). The deregulation of PI3K signaling pathways resulting from PTEN gene mutation on 10q23 at the level of LOH in at least 60% of GBM (37). PTEN genetic mutation is associated with the poor survival of patients with GBM (38). The p53 and PTEN signaling pathways are critical targets for GBM therapy, with advances in understanding their molecular mechanisms and interactions with other signaling networks being essential for improving treatment outcomes (39).

Inflammation associated with GBMs may induce dysfunctional responses to the brain microenvironment (40). An increase in inflammation can decrease the efficiency of cancer therapies and targeted therapies such as anti-VEGF drugs. Chronic inflammation in the brain will affect treatment delivery by altering the microenvironment and stimulating inflammatory adaptations (40). Previous research has shown that the Tie2-expressing monocyte population is pro-angiogenic, expressing relevant gene transcripts such as VEGF (41). Myeloid-derived suppressor cells (MDSCs) may also contribute to the integrity of the neo-endothelium of tumor vessels due to their expression of endothelial markers, such as CD31 and VEGF receptor, and their ability to morphologically resemble endothelial cells (42). The mutation in p53 promotes chronic inflammation in GBM, which is associated with a poor prognosis and high mortality rates (43). The primary target for upregulation by p53 gene mutation is the upregulation of C-C motif chemokine ligand-2 and tumor necrosis factor-α (TNF-α) expression. This upregulation is positively related to increased microglia and monocyte-derived immune cell infiltration, which may consequently promote inflammation in GBM, but may also inhibit treatment delivery and action (43).

The role of inflammation in decreasing the efficacy of targeted therapies may result from hypoxic conditions, suppressing the expression of cylindromatosis (CYLD), a tumor suppressor that regulates signaling pathways by acting as a deubiquitinating enzyme (44). The study conducted by Guo *et al* (44) found that suppression of CYLD was a critical aspect of inflammatory responses in the GBM microenvironment. Thus, CYLD may function as a tumor suppressor, which unergoes a loss of function, followed by suppression, in the presence of GBM. Furthermore, CYLD suppression may promote TNF-α and NF-κB activity downstream and act in a paracrine fashion to increase GBM tissue inflammation (44). This results in the promotion of angiogenesis and a reduction in anti-angiogenic agents, leading to the further supply of nutrients to the tumor and increasing its malignancy.

4. Physiological and therapeutic mechanisms of exercise in cancer

Physical activity and exercise decrease the risk of developing several types of cancer, including breast, colon, endometrial, kidney, bladder, esophageal and stomach cancers (12,45). Therefore, increased attention has been paid to exercise as a non-pharmacological intervention for patients with cancer (46). While the impact of exercise on the clinical outcomes of patients with cancer is indispensable, understanding the cellular and molecular mechanisms of exercise in cancer is warranted. Despite literature advocating for the inclusion of exercise into treatment strategies for patients with cancer across a variety of diagnoses, mechanistic studies have not adequately assessed this response in the GBM population, despite similarities in its pathology to other cancer types.

Exercise and cancer prevention. Even though the mechanism of the reduced risk and recurrence of cancer by exercise is not yet well known, it is suggested that exercise has a positive impact

on the TME through the regulation of cellular processes and tumor growth (47). It is proposed that exercise exerts several biological effects to moderate these processes, including insulin/glucose metabolism, immune function, inflammation, sex hormone concentration, oxidative stress, genomic instability and myokine release (47,48). Regular exercise decreases plasma insulin levels and insulin growth factor (IGF-1) which may reduce cancer proliferation by decreasing the activation of receptor tyrosine kinases (47). Obesity is also associated with the development of several types of cancer by the same biological mechanisms (48). Exercise plays a clear role in weight management by reducing body fat and decreasing the incidence of several types of cancer (48). Research indicates that physical activity and regular exercise decreases inflammation by reducing the levels of inflammatory cytokines, circulating C-reactive protein and TNF-α, and increasing the levels of anti-inflammatory myokines (49). Exercise also enhances immune system function, which may play a role in cancer prevention (48). Further studies are required however, to explore these mechanisms in the prevention of GBM.

Exercise and epigenetic modification. A variety of physiological adaptations are induced by exercise training, including the upregulation of signaling mechanisms for DNA replication, transcription and protein synthesis (50). Exercise may also play a critical role in attenuating cancer progression through epigenetic modification. A previous study demonstrated that anaerobic exercise increased p53 and PTEN expression, and decreased MDM2 expression, leading to the downregulation of the IGF-1 pathway in skin cancer (51). A recent study demonstrated that 4 weeks of high-intensity interval training (HIIT) reduced tumor volume and upregulated the mRNA expression of p53 in mouse models of breast cancer (52). These studies suggest that exercise may play a therapeutic role by enhancing the expression of the tumor-suppressor genes (TSGs), p53 and PTEN. The abnormal hypermethylation of TSGs is also a mediator of cancer development and progression with carcinogenesis (53). A review article showed that exercise adjusted the methylation status of TSGs and decreased promoter hypermethylation in nonmalignant breast cancer (54). It was also demonstrated that 6 months of moderate exercise also decreased methylation of the TSG L3MBTL1 in breast cancer, which is associated with a low risk of recurrence and mortality (55). A preclinical study revealed that regular exercise decreased circulating miRNA levels, including those of miR-21 in mice (56). An increase in in miR-21 expression is associated with the human estrogen receptor (ER)α in breast cancer and induces HIF-1α and VEGF expression in prostate cancer (57). Taken together, these studies suggest that exercise may play a preventive role and enhance targeted therapy in cancer by modifying epigenetic mechanisms.

Several studies have reported that exercise activates epigenetic mechanisms and regulates synaptic plasticity. A previous study demonstrated that an acute single bout of exercise has a positive impact on post-translational modifications of histone by decreasing histone deacetylase enzyme and increasing histone acetyltransferase enzyme in the hippocampus of rats (58). Furthermore, several studies have shown that exercise modulates epigenetic factors that regulate brain-derived neurotrophic factor (BDNF) expression and induces gene expression associated with synaptic plasticity in rats (59). It was previously demonstrated that 1-week wheel-running intervention increased the global acetylation of histone 3 in the hippocampus of mice, thereby, increasing the transcription of BDNF (60). Recent studies have demonstrated that patients with GBM exhibited reduced levels of BDNF in both their plasma and cerebrospinal fluid, potentially being associated with cognitive decline in GBM (61,62). Although several studies have shown that the adjuvant therapeutic role of exercise functions through epigenetic modification in patients with cancer (54), no studies to date have examined the therapeutic effect of exercise on epigenetic modification in patients with GBM, at least to the best of our knowledge. Additional research to replicate animal model findings in humans and explore the mechanistic effect of exercise within the TME is critical for patients with GBM.

Exercise and the RTK singling pathway. Previous studies have demonstrated that regular exercise inhibits PI3K/Akt/mTOR signaling and attenauates tumor growth in triple-negative breast cancer, which does not proliferate in response to the estrogen receptor, progesterone receptor, or EGFR/HER2/neu activation (63). Exercise appears to modify several systemic signal inputs, which leads to physiological adaptation of breast cancer TME and mTOR inhibition (47). A preclinical study revealed that exercise decreased tumor growth by inhibiting of PI3K/Akt/mTOR signaling and enhancing apoptotic signaling via caspase-3 and Bax in breast cancer models (64). Even though these data suggest that exercise inhibits the PI3K/Akt/mTOR pathway and enhances the TME in cancer, studies have not explored the effects of exercise on PI3K/Akt/mTOR in GBM.

Exercise and angiogenesis. Anti-angiogenic therapy directed at VEGF or its receptors has been approved for cancer treatment (65). However, despite their intended function of impeding blood supply to tumors, these agents can lead to hypoxia, potentially exacerbating tumor progression and resistance to treatment. The most effective role of exercise on the tumor is related to its impact on angiogenesis and vascular changes in the TME. It has been shown that exercise enhances tumor VEGF levels and angiogenesis (13). Exercise training has been shown to increase VEGF expression and tumor angiogenesis, and decrease tumor burden in a mammary cancer mouse model (66). The increased tumor vascularization and perfusion may decrease tumor hypoxia, increase drug delivery to the tumor and increase tumor response to radiation (13). A preclinical study revealed that exercise with tamoxifen and letrozole treatment reduced ERα, HIF-α, VEGF and miR-21 expression levels associated with a decreased tumor growth and increased vascularization in mouse breast cancer models (67). Another preclinical study demonstrated that miR-21 induced tumor vascularization by targeting PTEN, inducing the stimulation of AKT and ERK1/2 signaling pathways and enhancing HIF-1 and VEGF expression in prostate cancer cells (57). The anticipated outcome of exercise-induced stabilization of HIF-1 was an increase in metastatic spread. Contrary to expectations, voluntary wheel running in mice with prostate or breast cancer has been found to result in the opposite effect (68,69). However, a recent meta-analysis demonstrated that regular exercise did not significantly modify the number of metastatic foci or the

risk of developing metastasis in animal cancer models (70). Further research is warranted to fully determine the impact of exercise on hypoxia, angiogenesis and metastasis in cancer overall, with a specific focus on GBM.

Exercise and AMPK. It has been reported that regular exercise activates the AMPK pathway, which plays a significant role in regulating glucose uptake, glycogen synthesis and insulin sensitivity by skeletal muscle (71). The activation of AMPK may also suppress tumor growth by regulating aerobic glycolysis, imposing metabolic checkpoints and inhibiting cell growth (72). Further, it has been shown that AMPK activation plays a significant role in treating and preventing several types of cancer (73). For example, Lee *et al* (19) demonstrated that wogonin supplement, an AMPK activator, increased apoptosis and inhibited cell proliferation by increasing p53 and p21 expression in GBM cells. Another study demonstrated that regular exercise decreased the number and volume of hepatocellular tumors by enhancing the phosphorylation of AMPK and decreasing mTOR levels (74). However, several studies have found that in the late stage of breast and colorectal cancer, AMPK switches to a tumor promoter, enhancing cancer cell survival by protecting against metabolic, oxidative and genotoxic stresses (75-78). Therefore, the AMPK pathway appears to play an essential role in early-stage targeted therapy for patients with cancer. Further research is warranted in order to examine the effects of exercise on the AMPK pathway in cancer in general, and in GBM specifically.

Exercise and lactate metabolism. Research has indicated that 7 weeks of aerobic exercise reduces tumor growth, lactate concentration in the TME and tumor monocarboxylate transporter expression by modifying ER receptor α (79). Bacurau *et al* (80) found that aerobic exercise decreased carcinoma glucose consumption and lactate concentration. Lactate accumulation in the TME leads to angiogenesis and may inhibit cytotoxic immune T-cell activity (48). Regular exercise also has a positive effect on ALDH, which is implicated in the metabolic dysfunction of GBM (81). The effect of exercise on lactate and ALDH in cancer and GBM is not yet fully understood. Future research aimed at determining this relation is thus warranted.

Exercise and immune system function. Recent literature highlights the role of exercise in maintaining a healthy immune system in cancer (82). Regular exercise enhances immune surveillance to detect and eliminate abnormal cells before they develop into cancer (83,84). During acute exercise, tissue macrophages exhibit an increased antipathogen activity and enhanced recirculation of immunoglobulins, anti-inflammatory cytokines, neutrophils, natural killer (NK) cells, cytotoxic T-cells and immature B-cells, which are crucial for immune defense and metabolic health (83-86). Acute exercise facilitates the movement of innate immune cells and components between lymphoid tissues and the blood compartment. Although these changes are transient, their cumulative effect over time improves immunosurveillance against pathogens and cancer cells, while reducing systemic inflammation (83,84). Regular exercise also enhances the immune system in cancer indirectly by increasing vascularization, decreasing hypoxia, decreasing glucose consumption and lowering lactate production increasing infiltrating immune cells into the TME (82). Furthermore, infiltrating cytotoxic immune cells into the TME is a positive prognostic marker for cancer outcome and mortality (87). One potential mechanism through which exercise improves immune system function in solid tumors is by increasing NK cell recruitment and infiltration (88). A clinical study showed that acute intermittent exercise mobilizes NK cells into circulation in breast cancer patients to the same degree as age-matched healthy controls (89). Another study demonstrated that HIIT decreased tumor volume, enhanced metabolic health and increased the NK cell number in breast cancer models (90). Pedersen *et al* (91) demonstrated that voluntary wheel running in mice suppressed the tumor growth rate, associated with a significant number of NK cells and the release of IL-6 from exercising muscles and epinephrine from the adrenal glands. That study suggested that IL-6 from exercising muscle may play a role in recruiting NK cells to migrate into the TME. In addition, another study demonstrated that a combination of exercise and PD-L1 inhibitor may delay tumor progression, decrease tumor burden, decrease MDSCs, and increase NK cell activity in the preclinical cancer model (92), where MDSCs inhibit the infiltrating immune cells through PD-L1 that control the activity of the cytotoxic immune cells (93). The impact of this dysfunction on immune cell activity as a result of the tumor and TME requires further research on order to fully understand the interplay and regulation of cancer on immune health by exercise.

Exercise and cancer therapy. With an improvement in cancer management, the cancer mortality rate has declined since 1990 (1); however, this has led to an increase in the number of patients treated with cancer therapy, resulting in a greater number of reports of severe side-effects. As a result, cancer survivors commonly report limitations from the adverse side-effects of surgery, radiation and chemotherapy. Typical side-effects include neutropenia, cardiac toxicity, skeletal muscle dysfunction and fatigue (94), which impair the activities of daily living and compromise the QoL of patients with cancer. A previous study demonstrated that aerobic exercise plays a potential role in preventing and treating the cardiotoxic effects of doxorubicin through the improvement of cardiorespiratory fitness (95). Another study evaluating the effect of supervised exercise on cancer survivors demonstrated improved cardiorespiratory fitness, skeletal muscle strength and antioxidant capacity, and decreased levels of oxidative stress in patients with cancer (96). Another study revealed that aerobic exercise may reduce cognitive impairments by improving neuroplasticity and mitochondrial function in the brains of rats receiving doxorubicin treatment (97). Even though these data suggest that the pleiotropic adjuvant therapeutic effect of exercise enhances the pharmacodynamics of chemotherapy and alleviates the side-effects of radiotherapy in GBM, to the best of our knowledge, there are not studies available in the current literature which have explored the effects of exercise on the side-effects of temozolomide in GBM.

5. Role of exercise as an adjuvant therapy in GBM

Literature reviews have indicated that rehabilitation and physical activity have the potential to ameliorate cognitive

function, motor function and the QoL of patients with brain tumors (98,99). The European Association of Neuro-Oncology recommends that patients with brain tumors exercise in a rehabilitative and supervised setting (100); however, there are few evidence-based guidelines for rehabilitative exercise to reduce the loss of cognition, and improve the function and QoL of patients with GBM (101). Considering the abundance of evidence detailing the positive benefit of physical activity and exercise in other forms of cancer, the lack of evidence specific to GBM poses a significant challenge within exercise oncology settings (102).

Feasibility of exercise in GBM. For those studies which have examined the role of exercise as a non-pharmacological intervention in brain tumors, the results are promising. For example, inpatient rehabilitation has been shown to improve the functional performance, physical capacity and daily activity of patients with brain tumors and GBM (103,104). The Exercise for Neuro and Head and Neck Cancer Patients (ENHANCE) program revealed that 12 weeks of aerobic and strength training was feasible and improved psychological function, physical function and the QoL of patients with brain tumors (105). A controlled clinical trial demonstrated that 12 weeks of aerobic exercise was an effective, safe, and low-cost therapy for enhancing brain recovery by fostering white matter and hippocampal volume, and improving the reaction time in children with brain tumors (106). Similarly, a pilot randomized controlled trial demonstrated that a home-based exercise program was feasible and safe in patients with grade II and III gliomas (107). A previous clinical case report demonstrated that HIIT was feasible for a patient with GBM undergoing multimodal therapy (108). Finally, a qualitative study also demonstrated that combined exercise was a feasible and safe therapy for patients with GBM undergoing chemoradiotherapy (109). Cumulatively, these data suggest that exercise is safe, feasible and a potential adjuvant therapy for patients with GBM.

Exercise improves performance and quality of life of patients with GBM. A literature research revealed that rehabilitation interventions can enhance the QoL and functional outcomes of patients with glioma (98). Recently, Gehring *et al* (107) demonstrated that 6 months of home-based exercise training increased peak oxygen consumption by 7% in patients with brain tumors compared to a non-exercising control group. Furthermore, another study demonstrated that 12 weeks of combined training reduced waist circumference and improved grip strength and 30-sec sit-to-stand in brain tumor patients (105). A previous case report study revealed that a novel 60-week exercise training program improved walking ability, exercise performance, muscle strength and the QoL of patients with GBM actively undergoing radiotherapy (110). A pilot study demonstrated that intensive rehabilitation improved engagement in activities of daily living and physical function scores in patients who underwent the surgical resection of a brain tumor (111). Similarly, an observational clinical trial revealed that 12 weeks of an inpatient or outpatient rehabilitation program improved physical functioning scores in daily activities, prevented functional disability, and reduced symptoms in patients with GBM and brain tumors (112). These findings suggest that improved functional performance and physical capacity may reduce fatigue, promote psychological health and promote well-being, subsequently improving the QoL of affected patients (113). While these data suggest that exercise improves functional performance and the QoL of patients with GBM, further studies are required to elucidate the exercise effects on GBM (98). This includes identifying optimal exercise models, assessing motor and cognitive outcomes, evaluating the long-term training effects, and measuring the influence of motor and cognitive rehabilitation on the daily lives of patients.

Exercise improves the cognitive function of patients with GBM. Regular exercise training improves cognitive function and structure by enhancing neural plasticity, increasing BDNF, decreasing endogenous corticosteroids and pro-inflammatory cytokines, reducing oxidative stress, improving vascularization and blood flow, and increasing the levels of hormones beneficial to neural structure and function (114). However, the therapeutic role of exercise in alleviating cognitive impairment is not yet well understood in patients with GBM. A previous preclinical study demonstrated that 4 weeks of exercise improved memory and cognitive impairments in rats receiving oxaliplatin and 5-fluorouracil chemotherapy (115). Another preclinical study revealed that 5 weeks of aerobic exercise in healthy rats treated with radiotherapy alleviated cognitive impairment, relieved the impairment of hippocampal neurogenesis and attenuated the downregulation of BDNF (114). These data suggest that exercise aids in alleviating cognitive impairment in GBM and illuminates the primary mechanisms of therapeutic efficacy of exercise on cognitive function.

In humans, evidence exists to support the inclusion of exercise in the GBM population. A previous study reported significant improvements in various measures of cognitive function following exercise training in patients with neurology disease (116). Another study showcased that 12 weeks of combined exercise improved mental health, shortness of breath, psychological function, and symptom management for depression and anxiety in patients with brain tumors (117). A randomized controlled trial demonstrated that 6 months of home-based exercise training improved cognitive test performance and the patient-reported outcomes of patients with glioma (118). Moreover, a recent randomized controlled trial demonstrated that exercise coupled with monitor-augmented reality during radiotherapy effectively mitigated the decline in muscle strength and cognitive function in patients with high-grade gliomas (119). However, despite these positive effects, that trial reported no significant impact of exercise on BDNF levels (119). Given that the majority of studies have been conducted using animal models, further research is required to explore the effects of exercise on cognitive function and BDNF in patients with GBM, and to further elucidate the mechanisms contributing to the therapeutic effects of exercise on cognitive impairments in humans with GBM.

Exercise and the prognosis of patients with GBM. Initial research in preclinical animal models has suggested that exercise improves survival in GBM. For example, Lemke *et al* (120) found that exercise with temozolomide therapy significantly prolonged the survival of glioblastoma-bearing mice, reduced

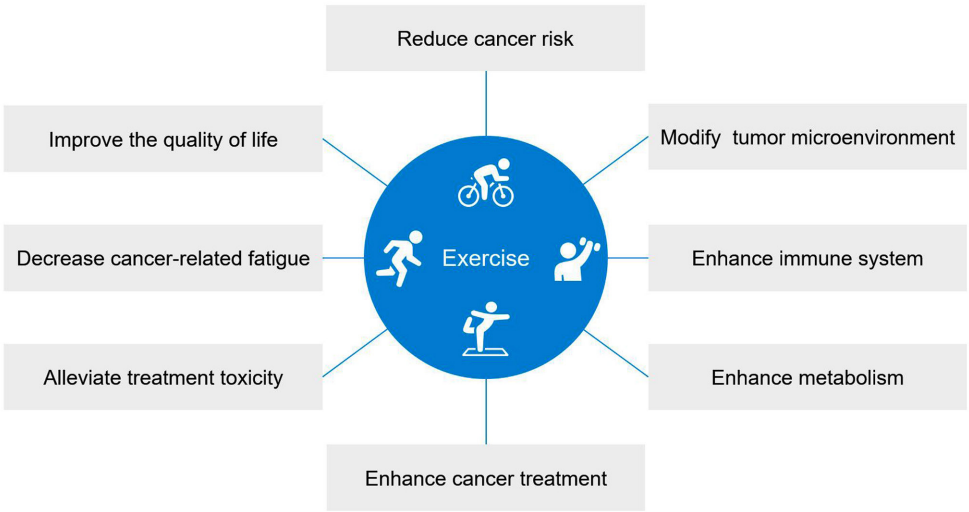

Figure 1. Schematic diagram depicting the effects of exercise training on patients with cancer.

tumor volume and invasiveness and prevented a significant loss of body mass. Another recent preclinical study revealed that voluntary exercise decreased the proliferation rate of tumor cells, delayed motor deterioration and supported the ability for self-care in a mouse model of glioma (121). It has been suggested that exercise increases BDNF in circulation which may attenuate tumor cell proliferation (60,114). The mechanisms of the protective role of exercise in brain tumors and GBM, however, are not yet fully understood, but may include physiological adaptations that modulate tumor progression and cancer therapy (122). A preclinical study demonstrated that aerobic exercise in mice infused with metastatic tumor cells regulated tight junction proteins in brain microvessels during metastasis and contributed to modulating BBB integrity, protecting the brain during metastatic progression (123).

As these data have been translated to humans, a previous observational study demonstrated that the performance status has prognostic value, associated with the survival rate and disease progression in patients with GBM (124). Moore *et al* (125) screened the health records of >300,000 individuals and found that physically active adolescents had a 35% lower risk of developing glioma than physically inactive individuals. Another study reported that patients with WHO grades III and IV malignant glioma who exercised more than 9 metabolic-equivalent (MET) hours/week had a median survival of 7.8 months longer than those who exercised <9 MET hours/week, suggesting that exercise may improve survival duration of patients with GBM (126). Additionally, the National Walkers' and Runners' Health Studies cohorts, which included >153,000 participants, demonstrated that both general physical activity (i.e., walking 19-37 km/week) and exercise (i.e., running 12-25 km/week) may reduce the risk of brain tumor mortality by 43.2% (127). These authors demonstrated that general exercise behavior is a strong independent predictor of survival rate in recurrent glioma (126). Preclinical studies have laid the foundation of evidence for the utility of exercise training to improve prognosis in animal models. The evidence available in humans has also begun to shed light on the positive effect of exercise training on prognosis in brain tumor patients. However, the data are limited and gaps in scientific understanding remain. Given what is known about other cancer types, additional research focused on exploring the mechanisms and protective role of exercise in GBM is required (45).

6. Exercise guidelines for cancer survivors

The American College of Sports Medicine (ACSM) and International Multidisciplinary Roundtable on Exercise and Cancer have recommended that each cancer patient should be physically active and avoid sedentary behavior (128). They concluded that physical activity and exercise training play a role in preventing various cancer types, improving longevity among cancer patients and enhancing common cancer-related health outcomes including cancer-related fatigue, physical functioning and health-related QoL (12,128). Current programming for cancer recommends moderate-intensity aerobic exercise for at least 30 min, three times per week; and resistance exercise for two sets of 8-15 repetitions at 60% of one repetition maximum, twice per week. However, these guidelines are created for cancer patients in general, not specifically for patients with GBM. Patients with GBM have a broad range of neurological and musculoskeletal impairments that need to be considered before commencing an exercise training program. Therefore, further studies are warranted to determine the optimal mode, intensity and frequency of exercise in this population, along with the appropriate time to initiate a program, given the unique treatment considerations regarding surgery, chemotherapy and radiation.

7. Conclusion and future perspectives

The pathogenesis of GBM has a variety of pathways that can be targeted by traditional cancer treatment and may be directly or indirectly influenced by exercise. The role of exercise in the cancer population has already been established in various other types of cancer, namely breast, prostate and colorectal cancers (Fig. 1). Furthermore, the complementary nature of exercise to traditional treatment renders this a lucrative pursuit for this cancer population.

In summary, it is generally considered safe for patients with GBM to participate in exercise and should be viewed as a viable option by medical practitioners and patients. The inclusion of this non-pharmacological form of therapy provides an avenue for an improved prognosis and QoL, while instilling healthy lifestyle behaviors in patients. Further research is warranted to understand the mechanistic effect of exercise on cellular processes impacted by cancer and its treatments, with a particular emphasis on the GBM population. Concrete guidelines are also necessary to guide clinicians and exercise physiologists on the most appropriate exercise mode, intensity and frequency to implement for their patients to maximize their rehabilitation. Finally, further research is necessary in order to understand the impact of exercise on novel forms of treatment in GBM, and cancer globally.

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Authors' contributions

SS and NH conceptualized the study, engaged in manuscript editing, reviewing and revision, and handled communications with the journal. DH and TO assisted with manuscript editing, reviewing and revision. All authors have reviewed and endorsed the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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