



# Looking at the Impact of Physical Activity on Glioblastomas Multiforme and Redox Metabolism <sup>†</sup>

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**Abstract:** When considering a disorder without tumor redox metabolism, it is important to focus on glioblastoma multiforme. These are malignant tumors originating in astrocytes and oligodendroglia. They are highly aggressive and develop rapidly, and for this reason death can occur a few months after diagnosis. This study aims to provide an overview of the potential of physical activity against the redox system in glioblastoma multiforme. A narrative review was used as a method to gain a pertinent understanding of the topic. To help this study carry out its investigation, a guided question was imputed into electronic databases such as Pubmed Central, Scielo and Scopus. Answers to the question “what is the influence of physical exercise on the redox metabolism of glioblastoma multiforme?” were chosen to compose the final sample of studies. The results reveal that knowledge of oxidative stress processes against glioblastomas can provide insights into the different managements that slow the progress of the disease and decrease its morbidity and mortality. A positive regulation of mRNA from antioxidant enzymes was corrected, suggesting autophagy, damaging an anti-invasive effect of the tumor. However, other authors did not observe a reduction in the tumor. Although divergent, the information is promising for the clinical management and quality of life of patients.

**Keywords:** multiform glioblastomas; redox system; physical activity



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## 1. Introduction

Cancer is an advanced disorder in cell metabolism, impairing the disordered proliferation of cells and causing physiological functioning and damage to organs. This problem is increasingly common in the world population, being responsible for great morbidity and mortality. The increasing aging of the population and other genetic and environmental factors are linked with the possible triggers of this disease [1].

Among the various molecular mechanisms that are altered in a tumor cell, oxidative stress stands out with the increase in reactive species, such as superoxide and hydroxyl anions. As a consequence, there is a promotion of damage in essential biomolecules for cell metabolism, such as DNA and RNA fragmentation and protein and lipid damage. In tumors, hypoxia and other stressors contribute to the high prevalence of reactive oxygen species (ROS) [2].

Although cancer management varies according to the type and morphology of the disease, its treatment is usually complex and causes considerable damage to the physical and mental well-being of patients. Considering this, several innovative therapies are investigated with a view to a new complementary approach. Alternative and non-pharmacological approaches are increasingly studied, with an emphasis on physical exercise. This type of

practice is related to a series of health benefits, such as reducing cardiovascular problems, releasing myokines and decreasing glycemic levels. In addition, there is a relationship between the increase in enzymatic antioxidant activity and activating systems for the restoration of homeostasis oxidative, obtained with the periodic practice of physical exercise [3,4].

Among the pathologies that present disorders in the redox metabolism of the previously mentioned tumors, multiform glioblastomas stand out. These malignant tumors originate in astrocytes and oligodendrocytes and are most common in adults. As they are highly aggressive and of rapid development, death can occur within a few months after diagnosis. Its cause is not fully elucidated in the scientific literature; however, it is known that its tumor cells have a specific type of mechanism related to redox metabolism, enabling its development [5].

As the central nervous system is highly sensitive to damage caused by ROS, and given the magnitude of this health problem, this study aims to provide an overview of the potential of physical activity against the redox system in glioblastomas multiformes. Thus, it will help in the understanding and management of future studies involving the clarification of metabolic pathways for this type of problem, as well as intervention proposals for this problem.

## 2. Materials and Methods

For the development of this research, a narrative literature review was adopted as the methodological process. This type of methodology allowed us to gather state-of-the-art material on relevant subjects and build a broad view of the theme, having in its results significant contributions to critical discussions about what the scientific literature addresses. Its structure is qualitative and descriptive, using scientific articles to build its scope.

The study's guiding question was "what is the influence of physical exercise on the redox metabolism of glioblastomas multiformes?" The bibliographic research took place in electronic databases for indexing articles and scientific journals, such as Pubmed Central, Scielo and Scopus. The collection of works took place in parallel from reading titles and abstracts.

This process took place between October and November 2020, prioritizing the election of recent works from the last five years, with relevant and innovative results. The preferred languages were Portuguese, English and Spanish. After this prior analysis, studies were selected after full reading, collecting the main findings that answered the question and the objective of this investigation.

These results were interpreted and critically correlated, building a broad essay on the subject, informing future researchers and health professionals. By using data obtained from studies already published and available, it was not necessary to submit this research to the Research Ethics Committee, nor to process the data with external judges.

## 3. Results and Discussion

Physical exercise has a diversity of benefits across a range of biological systems, positively affecting health, and the impacts on redox mechanisms are increasingly explored in this regard. In this context, the understanding of reactive species and oxidative stress is exalted, the first being produced naturally by metabolism, generated by organelles and complexes such as the mitochondrial electron transport chain, responsible for energy production that includes structural modification by redox reactions. This process is physiological and, for its balance, the antioxidant system plays a significant role [2,6].

When there is an excess production of free radicals, molecular damage can occur, such as cell damage and genetic material damage, characterizing oxidative stress, which plays a role in the genesis of several nosological events, and even chronic diseases [7]. In cases of cancer, several are under the effect of oxidative stress. This is often exacerbated by high metabolic and proliferative activity, which therefore accentuates the neoplastic behavior [1,8].

Considering this scenario, the impact of exercise against various cancers is investigated. Issues such as involvement in health promotion, such as overweight, psychological and social issues positively affect the general health status of these individuals and are well outlined in the literature [3,4,8]. However, studies that highlight the interesting participation of physical activity in cerebral redox metabolism deserve further attention. Due to the increase in  $O_2$  consumption, there is an increase in the concentration of ROS, and the brain tissue is markedly sensitive to oxidative stress. On the other hand, there is an increase in the production of neurotrophins, promoting, for example, neuroplasticity [9,10].

In the management of glioblastomas, this promotion of oxidative stress is presented as an attractive alternative to delay the progress of cancer. A study involving mice with glioblastomas evaluated the participation of physical exercise alone and as an adjuvant in drug treatment. Running for 45 min for five to seven days a week was revealed to decrease tumor growth; however, there was no influence on the survival of these animals, with its effect optimized when used with drug treatment [11].

One of the related mechanisms is the increase in reactive species capable of causing DNA damage and inducing cell death. Thus, it can also be associated with ways to control tumor proliferation, such as the oxidative stress generated by alkylating agents, a class of antineoplastics. Thus, the authors evaluated in vitro the activity of DHA, which works as an inducer of oxidative stress, aiming to understand the participation of stress in tumor involution. Upregulation of mRNA of antioxidant enzymes, and anti-glioma effects, as a suggestion of autophagy, resulting in an anti-invasive effect were observed [11].

However, unlike food deprivation, in which there is evidence of protection for normal cells against high doses of chemotherapy, but not cancer cells [12], which enables an increase in the concentration of chemotherapy without causing further damage to healthy structures, the aforementioned authors did not identify such a response regarding the results of physical exercise.

In the case of gliomas, especially glioblastomas, knowledge of oxidative stress processes can provide insights into different managements that delay the progress of the disease and reduce its morbidity and mortality [13]. In 2016, the results of an investigation of two women with glioblastoma multiforme for 12 weeks, submitted to a program of two sessions of aerobic and resistance activities, were also published. Exercise was well tolerated and provided a decrease in morbidity, promoted mental health and physical conditioning, decreased insomnia and improved their depressive and disabling condition. However, oxygen consumption varied between the two patients [14].

As for survival, another study aimed to investigate the effects of this activity in a 33-year-old man with glioblastoma multiforme, applying high-impact exercises for 21 months. No tumor reduction was identified; however the patient died 24 months after diagnosis, a period above the best median survival in most trials, which is around 15–18 months. This practice helped to establish a better quality of life and is a factor in promoting the improvement of a patient's general condition, as well as reducing the morbidity of the disease [15].

Against this result, a project involving 243 patients, a larger number of people compared to the previous study, with glioblastomas multiformes was followed for about 27 months, aiming to identify markers that optimize the treatment and survival of recurrent malignant glioma cases. This study showed that the regular practice of high-intensity physical activity is linked to a significantly higher survival rate for these patients. These authors also mention the regulation of several factors such as the concentration of steroid hormones, the immune system and angiogenic factors that interfere in the tumor microenvironment [16].

#### 4. Conclusions

The research revealed that the impact of physical exercise, especially intense sets, overloads the redox metabolism in the system in which the glioblastoma is inserted, leading to tumor damage. Studies reporting a reduction in tumor tissue and a consequent delay

in the development of the disease were identified. However, investigations are needed to better elucidate the biochemical and molecular processes and their influence on different stages of the pathological process, since not all studies have identified tumor regression or increased survival. However, the practice of physical activity represented a relevant therapeutic alternative, not only for the microenvironment and delay of glioblastomas, but also for improving the quality of life and general condition of those affected by this problem.

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