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A STUDY OF THE RELATIONSHIP BETWEEN CARBOHYDRATE RESTRICTION AND THE TREATMENT OF GLIOBLASTOMA: A LITERATURE REVIEW

ESTUDO DA RELAÇÃO ENTRE RESTRIÇÃO DE CARBOIDRATOS E O TRATAMENTO DE GLIOBLASTOMA: UMA REVISÃO BIBLIOGRÁFICA

ESTUDIO DE LA RELACIÓN ENTRE LA RESTRICCIÓN DE CARBOHIDRATOS Y EL TRATAMIENTO DEL GLIOBLASTOMA: UNA REVISIÓN DE LA LITERATURA

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ABSTRACT

5 years of 5%. Because it is a difficult diagnosis to treat, it motivates several lines of research to optimize the currently proposed standard treatment, which consists of chemoradiation and surgical resection, when possible. The reduced use of the citric acid cycle and mitochondrial oxidative phosphorylation for energy production in cancer cells that primarily use anaerobic glycolysis, even in the presence of oxygen, characterizes the Warburg effect, which justifies the use of diets with restricted carbohydrate intake that generate ketosis to reduce energy intake and consequently delay tumor progression, since healthy cells are able to receive energy more efficiently from fatty acids. The conclusions of 21 articles selected from databases (PubMed and LILACS) related to diets with reduced carbohydrate intake and the treatment of glioblastoma were correlated, as well as seeking to analyze the secondary variables present in clinical studies. Thus, the complexity of conducting research on this topic becomes clear, and the need for more robust studies, especially clinical ones, is proposed to allow for a meta-analysis of the subject in order to define therapeutic approaches that may include or rule out the implementation of carbohydrate-restricted diets in the treatment of glioblastoma.

Keywords: Glioblastoma. Ketogenic Diet. Atkins Diet. Warburg Effect. Carbohydrate Restriction.

RESUMO

5 anos de 5%. Por ser um diagnóstico de difícil tratamento, motiva diversas linhas de pesquisa para otimizar o tratamento padrão atualmente proposto que consiste em quimiorradiação e ressecção cirúrgica, quando há esta possibilidade. A redução da utilização do ciclo do ácido cítrico e da fosforilação oxidativa mitocondrial para a produção de energia em células cancerosas que utilizam prioritariamente a glicólise anaeróbica, mesmo na presença de oxigênio, caracteriza o efeito Warburg, que fundamenta a utilização de dietas com restrição na ingestão de carboidratos geradoras de cetose para diminuir o aporte energético e consequentemente retardar a progressão tumoral, uma vez que as células

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sadias são capazes de receber aporte energético com maior eficiência de ácidos graxos. Relacionaram-se as conclusões de 21 artigos selecionados em bases de dados (PubMed e LILACS) relacionados a dietas com diminuição da ingestão de carboidratos e o tratamento de glioblastoma, assim como busca analisar as variáveis secundárias presentes nos estudos clínicos. Dessa maneira, compreende-se a complexidade de execução das pesquisas acerca do tema exposto e propõe-se a necessidade de estudos, sobretudo clínicos, mais robustos que permitam uma meta-análise do tema para definir condutas terapêuticas que possam incluir ou descartar a implementação de dietas com restrição de carboidratos no tratamento de glioblastoma.

Palavras-chave: Glioblastoma. Dieta Cetogênica. Dieta Atkins. Efeito Warburg. Restrição de Carboidratos.

RESUMEN

5 años de 5%. Debido a su difícil tratamiento, se motivan diversas líneas de investigación para optimizar el tratamiento estándar propuesto, que consiste en quimiorradiación y resección quirúrgica, cuando sea posible. La reducción del uso del ciclo del ácido cítrico y la fosforilación oxidativa mitocondrial para la producción de energía en células cancerosas que utilizan principalmente la glucólisis anaeróbica, incluso en presencia de oxígeno, caracteriza el efecto Warburg, lo que justifica el uso de dietas con ingesta restringida de carbohidratos que generan cetosis para reducir la ingesta energética y, en consecuencia, retrasar la progresión tumoral, ya que las células sanas pueden recibir energía de los ácidos grasos de forma más eficiente. Se correlacionaron las conclusiones de 21 artículos seleccionados de bases de datos (PubMed y LILACS) relacionados con dietas con ingesta reducida de carbohidratos y el tratamiento del glioblastoma, y se buscó analizar las variables secundarias presentes en estudios clínicos. Por lo tanto, se hace evidente la complejidad de la investigación sobre este tema, y se propone la necesidad de estudios más sólidos, especialmente clínicos, que permitan un metaanálisis del tema y definan enfoques terapéuticos que puedan incluir o descartar la implementación de dietas con restricción de carbohidratos en el tratamiento del glioblastoma.

Palabras clave: Glioblastoma. Dieta Cetogénica. Dieta Atkins. Efecto Warburg. Restricción de Carbohidratos.

1 INTRODUCTION

1.1 GLYOMAS

Gliomas are classified into different types of tumors according to their glial lineages, including astrocytomas, oligodendrogliomas, mixed oligoastrocytomas, ependymomas, and several less common types of glioneuronal tumors[1]. Astrocytic brain tumors are primary CNS tumors derived from astrocytes. Astrocytes provide structural and metabolic support to neurons, regulate ion concentrations in the extracellular space, modulate synaptic transmissions, release neurotransmitters, compose the blood-brain barrier, among other functions[2].

The WHO classifies astrocytic tumors into 4 classes, according to the degree of aggressiveness (Table 1), and low-grade astrocytomas (I and II) tend to be present in younger patients and have a better prognosis. High-grade astrocytomas (III and IV) typically present in older patients and the prognosis is worse[2]. Glioblastoma multiforme (GBM) is considered grade IV, since it is highly aggressive, with a mean survival rate of 15 months[3] and a 5-year survival rate of 5%[4].

Table 1

Classification of glioma subtypes according to their histological characteristics by the World Health Organization

Degree	Tumor histology	Subtype according to Histology
I	Benign, well set	Pilocytic Astrocytoma
II	Diffuse infiltration and high proliferation	Diffuse Astrocytoma, Oligodendroglioma, Oligoastrocytoma
III	Very infiltrative and with a lot of proliferation	Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Oligodendroglioma Anaplastic
IV	Very infiltrative, high cell and vascular proliferation, necrosis, hemorrhage	Glioblastoma multiforme

Source: adapted from JONES & HOLLAND, 2011.

Macroscopically, GBM denotes a poorly delimited expansive mass in the white matter of a cerebral hemisphere with central necrosis, which may affect most of the tumor. Cysts and hemorrhages may be present, as well as peritumoral edema and midline deviation, with hernias. In some cases, the tumor infiltrates the corpus callosum, passing into the contralateral hemisphere forming a pattern called "butterfly wing tumor." Histopathologically, GBM presents cellular atypia exhibiting cells of different sizes and degrees of variation. Some cells have 2 bipolar extensions, resembling glioblasts - embryonic cells of the neural tube that give the tumor its name. Grade IV astrocytomas also present vascular proliferation, with an increase in the number of capillaries, both in the tumor and in the adjacent nervous tissue. These capillaries resemble the renal glomeruli, which is why they are called pseudo-glomeruli. The endothelial cells of the pseudoglomeruli are numerous and have swollen nuclei, which usually leads to thrombosis and consequent coagulative necrosis. There is also a high mitotic activity and infiltrative capacity of tumor cells that generates the poorly defined characteristic of GBM[5].

The pathophysiology of GBMs, as well as other brain tumors, is related to a metabolic disorder of tumor cells, so that cancer cells, in order to maintain a high mitotic rhythm, reduce the use of the citric acid cycle and mitochondrial oxidative phosphorylation for energy production and, instead, use anaerobic glycolysis as a priority. even in the presence of oxygen. This change in the pattern of obtaining cellular energy increases the glucose consumption of tumor cells and is called the "Warburg Effect", described in 1927 by the German scientist Otto Warburg[6].

In view of the Warburg effect and the pathophysiological characteristics of GBM, many researchers question alternatives that can help in the treatment of GBM, since current therapeutic measures do not provide a cure or considerable survival in the vast majority of cases. One of the current pathways is based on the fact that GBMs use glucose at a much higher intensity than the normal cortex and in states of prolonged glucose deprivation, normal brain cells metabolize ketone bodies derived from fatty acids to obtain energy instead of glucose, while tumor cells are barely able to do so. making them depend on glucose and glycolysis to survive. The energy delivery route of gliomas has a much lower yield than that of eutrophic cells, leading to a much higher need for glucose[7]. This makes tumor cells vulnerable to glucose-restriction therapies[8].

1.2 CARBOHYDRATE RESTRICTION AND KETOSIS

When carbohydrates are eliminated from the diet, either in fasting or low carbohydrate intake, energy can be obtained from the oxidation of fatty acids that occurs within the liver. This process generates ketone bodies (acetoacetate, hydroxybutyrate, and acetone) that are transported to the tissues where they are converted into acetyl-coenzyme A, which serves as a substrate in the citric acid cycle[9]. The state of use of this alternative pathway of obtaining cellular energy is called ketosis or ketone state, so that ketone bodies are an alternative energy source for the cells of the cortex, while tumor cells, due to dysfunctions resulting from their mutations, have mitochondria that are incapable of this process and generate many reactive species during the process, leading to apoptosis[10].

2 OBJECTIVES

2.1 GENERAL OBJECTIVE

To relate different conclusions about diets with reduced carbohydrate intake, in addition to CD proposed as classic, as alternatives to complementary treatment of patients with diagnosed GBM, as well as to perceive the conclusions about the applicability of CD and its variations with effectiveness in the state of ketosis, with variables such as palatability, tolerance and maintenance of diets.

2.2 SPECIFIC OBJECTIVES

- Analyze the main difficulties in carrying out the clinical studies carried out so far (August/2022);
- To consolidate the existing conclusions and compare these conclusions with what there is research on the subject in other educational institutions after the publication of the article by the Laboratory of Cell Biology of Gliomas of the Department of Cell Biology, Embryology and Genetics, with a view to valuing local science;
- Use medical-scientific knowledge platforms to signal conclusions of topics studied in different scenarios of pre-clinical, clinical and review studies.

3 WORK METHODOLOGY

A search of 21 articles selected from the related search of the terms "Diet, Ketogenic" and its variations suggested by the Medical Subject Headings (MeSH) was conducted; as well as the keywords "Glioblastomas", "Astrocytoma, Grade IV", "Glioblastoma Multiforme",

"Giant Cell Glioblastomas" and their variations; in addition to the terms "Diet, High Protein Low Carbohydrate", "Low-Carbohydrate", "Atkins Diet", "High-Protein Carbohydrate - Restricted Diets" and their variations in the PubMed and LILACS databases.

The inclusion criteria were the year of publication after 2014, written language, English, and Portuguese. The exclusion criteria were: unavailability of the full article on online platforms for the online availability of scientific knowledge and single case report studies due to its low impact on the scale of evidence and conclusions redundant to systematic review studies and laboratory tests.

After searching on knowledge platforms and reading the abstracts of the papers initially listed, the research proceeded with the full reading of each selected article and correlation of its results.

4 RESULTS AND DISCUSSION

4.1 PRECLINICAL STUDIES

Preclinical studies trace a path for the use of carbohydrate-restricted diets, both the ketogenic diet with different proportions [11,12,13,14] and the supplemented high-fat low-carbohydrate (sHFLC)[15] diet, in the adjunct treatment to the measures already implemented (radiochemotherapy). Although studies sometimes evaluate the same diet, as in the case of the ketogenic diet, they conclude different variables, since one study pointed to immune-enhancing effects, especially of Th1 and NK[11] cells, on tumor control while another study pointed to synergy with chemotherapy drugs in interrupting tumor migration[12]. There was also a histoanatomical correlation of the effect of CD, so that astrocytes were pointed out as the main cellular target of CD with greater synaptic participation in the region of the striatum[13]. The interaction of CD with Bevacizumab has also been shown to be beneficial for prolonging survival[14]. Thus, classic CD was promising in 4 preclinical studies, each of which listed a particularly beneficial characteristic of the association with standard care.

Other diets are being studied to serve as an adjuvant treatment to the one already applied clinically, such as sHLFC. Basically, the theory of this diet is also based on Warburg's effect and the state of ketosis, but his suggestion is due to the fact that this diet is more nutritionally complete, more flexible and palatable, due to the implementation of proteins and supplementation with medium-chain triglycerides[15]. Following the hypoglycemic logic, the study also compares the effects of metformin - a drug that acts to reduce hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, increasing tissue sensitivity to

insulin and delaying intestinal glucose absorption[16], when associated or not with CD and sHLFC, so that there was no synergistic effect between the measures[15].

However, there is no consensus among preclinical studies about the synergy of carbohydrate-restricted diets, since 2 studies found adaptive mechanisms of GBM to decrease glucose availability[17,18]. One of them evaluated the use of fatty acids as an energy substrate in 9L and RG2 tumor models and found values close to those of the human brain of oxidative metabolism made by tumors in vivo, demonstrating that tumors have a certain tumor flexibility capable of maintaining their mitotic rhythm. The authors comment on the difference in the time of insertion of tumor lines in mice, a factor that brings this study closer to reality, since patients do not start carbohydrate restriction immediately after the appearance of GBM, but after diagnosis, with a variable time that can take weeks to months[17]. The other study that points to the inefficacy of CD as an adjuvant therapy to the treatment of GBM denotes a decrease in tumor survival (of the U87 lineage, different from the tumor lines of the previous study) under the effect of a fatty acid oxidation inhibitor, with negative results in the survival rate of mice submitted to unrestricted CD, indicating the use of fatty acids for energy by GBM[18].

4.2 CLINICAL STUDIES

Clinical studies do not seem as promising as preclinical studies in their main objective of prolonging patient survival, as well as revealing important limitations related to patient adherence to studies until their conclusion. Studies that use CD have high rates of patient dropout. A study involving 15 patients undergoing a 3:1 CO with 10 patients completing the study generated secondary conclusions to those initially proposed, since the survival rate was the same as that found in patients who did not undergo any intervention[19]. Similarly, another study involving the implementation of CD, initially liquid and after two weeks solid with medium-chain triglyceride emulsions, obtained a survival rate compatible with the expectations of patients who do not undergo any specific diet[20]. In addition, another study with the implementation of the more classic CD following the 4:1 ratio, reached a mean survival rate of 12.8 months, with no increase in survival expectancy[21].

In all the clinical studies cited, the number of patients who finish the research is very small, especially in a study in which only 3 patients completed the study[22]. In this case, the conclusions point to the perceptions related to patient dropouts, as all 4 articles [19,20,21,22] qualify quality of life as a fundamental factor for patients and their families. As highlighted by

the clinical trials, GBM is considered an end-of-life certificate and most patients are not willing to spend their last days following an extremely restrictive diet that isolates them in their daily lives, making it impossible to socialize around a meal. In addition, the need for caregivers, partners or companions is a limiting factor for certain people who are unable to have a companion for all the necessary moments in their food preparation. Therefore, the applicability of CD is determined by the condition of the study or the patient in having aid for the preparation and maintenance of CD, as well as by the palatability offered by the diet. In addition, many patients reported intestinal discomfort, constipation, feeling hungry, nausea, vomiting and dizziness, although these symptoms may be caused by chemoradiation and by the pathological condition itself, and it is not possible to say with absolute certainty whether or not they are due to CD.

Another diet demonstrated greater adherence (96.6%) until the conclusion of the study in 29 patients. The Atkins diet involves a greater participation of proteins as an energy substrate and has greater palatability reported by patients, with the potential to generate ketosis, as well as CD. In this way, the study tries to correlate the survival of patients with a survival predictor: O^6 methylguanine-DNA methyltransferase (MGMT), but the number of patients with survival analysis is small and makes percentage analysis difficult. Therefore, this diet is pointed out as promising for studies with a larger number of participants[23].

4.3 PUBLISHED REVIEWS

The reviews follow the trend of clinical studies to adjust the expectation about CD at a lower level in relation to the results of preclinical studies, as well as signal more flexible and applicable paths for implementing a diet that brings the patient's blood glucose to lower levels.

New variables were added in relation to *in vivo* studies, both the psychosocial factors related to patients following CD in a strict way, which directly impacts the motivation, discipline and need for strict guidance from a nutritionist, and the interaction with corticosteroids used in the treatment to reduce cerebral edema and reduce the symptoms of patients with consequent increase in blood glucose and decreased efficacy of CD in generating ketosis[24 25].

Although some associations are positive in *in vivo* studies, their reproduction is not recommended clinically in humans, as is the case with calorie restriction associated with CD in order to enhance ketosis. Since the review of preclinical studies and case reports[25]

suggests this as a possibility to circumvent the effect of corticosteroids that, if withdrawn, impact a significant decrease in the quality of life of patients. However, another review, from 2018, states that body weight should be maintained, as weight loss and malnutrition in GBM patients are associated with a worse response to therapies, more adverse effects, complications, short mean survival, and poor quality of life. This suggests a concept of balance between the efficacy in generating ketosis and the feasibility of implementing dietary characteristics[26].

A review involving preclinical and clinical studies from 2020 traces the same trend already explained, because even though the survival rate was perceived in 17 of the 24 preclinical studies reviewed, the 4 clinical studies have great possibilities of bias. Thus, it is necessary to analyze the low number of patients followed, which makes it difficult to draw a percentage with a concrete reflection on reality. Also, the search of patients for various substances and alternative treatments in order to find a cure, which creates variables not analyzed in the studies. As well as the influence of corticosteroid therapy, implemented in standard treatment, which can decrease the effectiveness of CD in generating ketosis. Furthermore, the onset of CD is usually days or weeks after the diagnosis of GBM in real patients, unlike what is usually analyzed in preclinical studies that start CD at a time very close to tumor insertion. In addition, the guarantee of full follow-up of patients with CD is an important limiting factor, since many patients relate the diet to the side effects experienced during the treatment process and withdraw from the study[27].

Two reviews [28, 29] are dedicated to clarifying the influence of hyperglycemia as an independent factor of poor prognosis for the survival rate in patients with GBM, even reducing by half the mean survival in patients from a cohort of 367 patients[30]. Thus, not only CD but habits and diets with the potential to lower blood glucose could be suggested as protective factors for patients during treatment, and it is important to reduce carbohydrate intake, since the use of corticosteroids usually raises blood glucose, a fact that in patients who continue to eat high levels of carbohydrates can lead to recurrent hyperglycemia (determined as a risk factor for lower survival) [28, 29].

In general, preclinical studies determine more restrictive and rigid measures. On the other hand, clinical studies demonstrate the inapplicability of these measures due to a sum of factors added to the complexity of establishing in humans the same effects generated *in vivo* and *in vitro*, such as, for example, the need for a strong bond between researchers and patients to maximize patient motivation and the domestic support of a family member or friend

to help the patient overcome physical difficulties. cognitive and psychosocial aspects of the WBG. In this sense, a review tried to relate several dietary interventions already studied with the aim of generating ketosis with the use of the Warburg effect. Thus, unlike what some preclinical studies pointed to a classic, rigid CD with exact measurements of long-chain fatty acids and even a calorie deficit, clinical studies have seen more advantages in alternative diets such as diets with medium-chain triglyceride oil that provide more ketones per kilocalorie and enter the circulation more readily and the Atkins diet that is considered more flexible, applicable, palatable, and tolerable by patients with CD-like efficacy in generating ketosis. Thus, the concept cited by all reviews of balance between efficacy and viability is better contemplated by diets that are not necessarily CO[31].

The search for a cure for GBM instigates patients to undergo several processes with or without scientific recognition and this is pointed out as a probable generator of bias in the reviews[27,32], but it also drives the research of several substances that could complement the standard treatment, such as penicillamine, vitamin A, vitamin C, selenium, boswellic acid oil and curcumin, which have studies on their therapeutic use in cases of GBM. However, until the publication of the present study, there were no studies that support the clinical use of these substances, so that there are ongoing studies to understand their mechanisms[31].

4.4 STUDENT LEARNING

It is worth emphasizing, in addition to the better understanding related to the revised theme for the preparation of the study, the importance of the scientific initiation project for the critical sense and familiarity with scientific journals of the beneficiary, since it becomes increasingly necessary to critically read studies in the midst of so much circulating misinformation masked as science, especially in the field of medicine, who suffers daily attacks from those who do not understand the process of evidence-based analysis and continues to perpetuate bad practices, with consequent harm to their patients.

5 CONCLUSIONS

Most studies point to a positive interaction between the restriction of carbohydrate consumption and the standard treatment established for GBM, so that other diets, in addition to CD, have been gaining greater attention and have a promising future when it comes to applicability and efficacy in generating ketosis to induce the Warburg effect.

Preclinical studies, although without consensus[17,18], point to promising paths of CD

and alternatives, such as sHFLC[15], as synergists to chemoradiation in the treatment of GBM. However, preclinical studies do not find support in clinical studies carried out so far for the increase in the survival rate[19,20,21,222], the main objective of dietary measurement, as well as variables increased in human studies not perceptible in *in vitro* and *in vivo studies,* as the psychosocial factors linked to the maintenance of patients in the studies, had a decisive weight in the high dropout rate of the studies that did not allow an absolute analysis of the results. In addition, review studies reject the idea of calorie restriction proposed by some preclinical studies in patients with a consumptive syndrome, since weight loss is related to worse prognosis and higher chances of complications in patients with GBM [32,33].

In this scenario, one of the most cited variables in the review studies, as it was present in all the clinical studies analyzed, is quality of life. It was noticed that the efficiency of the diets should be linked to their potential for application, so that more restrictive diets with recipes that are difficult to prepare had a higher number of dropouts in their studies, while the Atkins diet (considered a more flexible and palatable diet) obtained good numbers regarding the number of patients who finished the study and state of ketosis during the process. The presence of a friend, family member or partner was decisive for the completion of the diets and maintenance of the patients' motivation, being a characteristic listed with a decisive role in the quality of life of the patients[20,22].

That said, the mechanisms established as beneficial need further studies for complete elucidation, since not only the state of ketosis proved to be adjuvant to the standard treatment, but also the maintenance of euglycemia in patients implies a higher survival rate when compared to patients with recurrent hyperglycemia. Thus, a diet that contributes less to the increase in blood glucose (already caused by the effect of corticosteroid therapy implicit in the treatment and responsible for improving the quality of life of patients during the process) is necessary as a prophylactic measure for the recurrent increase in blood glucose in these patients[28, 29].

Nevertheless, this is a literature review with its limitations, which implies the need for larger studies, with more refined methodologies in order to determine with certainty and/or recommend carbohydrate-restricted diets for the adjunct treatment of GBM.

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