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Low-carbohydrate diet in glioblastoma treatment – mechanism of action and safety

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ABSTRACT

Gliomas are primary neuroepithelial neoplasms, i.e. originating from the central nervous system. They account for about 30-40% of brain tumors. 40 to 90% of gliomas are malignant neoplasms. Conventional therapeutic approaches often fail to provide cure or long-term remission. An additional factor supporting the treatment may be a diet based on changes in the metabolic environment of the body.

Healthy cells have the ability to change from glucose to ketone bodies as their main source of energy. It is an evolutionary adaptation to food scarcity that allows survival during extreme changes in the environment. Unlike normal neuronal and glia cells, which easily use ketone bodies (β-oxybate) for energy, brain tumors are highly dependent on glycolysis. The condition for the flexible transition of cells from glucose sources to ketone bodies is a correct genome and mitochondria. The situation that limits this possibility are cancer mutations. An approach to treating brain tumors that uses the metabolic flexibility of healthy brain cells at the expense of cancer cells could become the future for extending the life of this group of patients. Studies in both animal and human models confirm the benefits of implementing a low-carbohydrate diet in the treatment of glioblastoma.

This chapter summarizes the latest reports in this area. A low-carbohydrate diet brings not only benefits such as reduction of tumor size and prolonged survival of cancer patients, but also many doubts about the safety of its long-term use due to malnutrition, deficiencies and changes in the intestinal microflora.

INTRODUCTION

2% of all cancers are primary brain tumors and 30-40% of them are gliomas. Most often, gliomas are found in adults between the ages of 40 and 65. Ratio male-female is 6:4 (Zülch, 1986). About 50% of gliomas in adults are glioblastomas (Schneider, 2010). Glioma arising from the glial group is in four grade and the IV grade of glioma is glioblastoma which is the most aggressive form. Glioblastoma (GBM) is account about for over 82% of all malignant gliomas (Varshneya, 2015). The etiology of GMB for-mation is unknown. It is suspected that both endogenous and exogenous factors may play a role. The incidence of the disease depends on age, sex, genetic factors, origin, exposure to infections, viruses, radiation, exposure to certain chemicals and diet (McLean, 2005; Idowu1, 2008).

The standard therapy in the treatment of glioblastoma is maximum excision followed by radiation and chemotherapy (temozolomide) (Martin, 2020). Medium survival after diagnosis, it is about 15 months. After treatment, it is approx. 5 years, and after treatment and relapse, it is about 25 months. Therefore, there is an ever increasing need to develop new treatments and prevention of glioblastoma that can accompany standard procedures (Klein, 2020). Recent research indicates alternative methods such as progesterone therapy or nutritional therapy that can inhibit angiogenesis in cancer glial cells while inhibiting the growth of a malignant tumor.

Glioblastoma cells, unlike normal cortical cells of the brain, are much more sensitive to changes in the level of glucose in the body. When there is a very low blood glucose level in the blood serum, e.g. due to starvation, healthy brain cells use ketone bodies as a source of energy, while this metabolic pathway is unavailable for glioblastoma cells (Klein, 2020). Impaired metabolic pathways of cancer cells are described in the 1950s by Otto Warburg. The differences in the use of glucose resources between cancer cells and healthy cells were referred to as the "Warburg Effect". It concerns genetic changes related to the use of glucose in the process of glycolysis in cancer cells. The metabolic differences may be related to the loss of p53, followed by an increase in the activity of serine-threonine kinase (Akt), which results in the use of excess ATP (Abdelwahab, 2012). Mutations in cancer cells can be used to combat them by altering the metabolic environment. Reduced glucose levels and increased ketone bodies prevent proliferation and inhibit the growth rate of GMB cells in animal and human models (Martuscello, 2016; Syfried, 2011). Significant

reduction in environmental glucose levels causes apoptosis of GMB cells, but not of normal brain cells. Additionally, high levels of ketone bodies inhibit the growth of GMB on human cell lines. It can therefore be assumed that both low glucose levels and high ketone bodies have a beneficial effect in the treatment of glioblastoma, while their synergistic effect is most beneficial (Syfried, 2011; Mukherjee, 2004). Caloric restrictions are an additional factor supporting the nutritional treatment of KD. The combination of nutritional ketosis and calorie reduction has a pro-apoptotic, anti-angiogenic, and anti-inflammatory effect, reducing the expression of the mTOR effector in mice with an experimental malignant glioma. This mechanism reduces tumor size and growth and increases rodent survival (Klein, 2020). Some studies suggest that nutritional ketosis may reduce tumor metastasis (Poff, 2015). It is also known that ketosis increases the sensitivity of cancer cells to chemotherapy and radiotherapy (Klement, 2018). It has been proven that during KD, low insulin and IGF-1 levels inhibit the PI3K/AKT signaling pathway, which promotes apoptosis, reduces proliferation and angiogenesis of cancer cells (Pondel, 2020). In contrast, high glucose levels cause tumor growth and stimulate angiogenesis, and prolong tumor life in mice (Seyfried, 2012; Mukherjee, 2004). Patients with GMB showing hyperglycemia have shortened survival times (Derr, 2009).

To induce a state of ketosis, it is important to supply carbohydrates in the diet. Among the diets, we distinguish high-carbohydrate diets, the energy of which comes from carbohydrates in more than 45%, from 26-44% of a medium-carbohydrate diet, less than 26% are low-carbohydrate diets and very low-carbohydrate diets contain less than 10% of carbohydrates from total energy (Oh, 2020). A low-carbohydrate diet is one that provides 20-60 grams of carbohydrates per day. Among low-carbohydrate diets, we can distinguish the Atkins diet and various ketogenic diets (KD) (Last, 2006). The Atkins diet was created in 1970 and is less restrictive with regard to the amount of calories, proteins or fats consumed, although about 65% of the energy requirement should be in the form of fat (Kossoff, 2008). Among KD, we can distinguish the classic 4: 1 form, the ketogenic MCT (Medium Chain Triglycerides) diet and the ketogenic diet with a low glycemic index (IG). KD 4: 1 should contain 90% energy as fat, for KD MCT is 73% (including 30-60% medium chain triglycerides) (McLean, 2004). A low GI KD diet should contain about 60% energy from fat, and carbohydrate sources should have a GI lower than 50 (Neal, 2017). Initially, to achieve the state of nutritional ketosis, i.e. the concentration of ketone bodies in the range of 1-7 mM in the blood serum, should be consume up to 20 grams of carbohydrates a day, then this amount can be increased to 50 grams (Pondel, 2020). This level of ketone bodies does not change the pH of the blood. Low blood glucose concentration causes the body to produce small amounts of insulin and increased amounts of glucagon, which in turn leads to the use of free fatty acids (FFA) released together with glycerol from adipose tissue by adrenaline as a result of lipase (Longo, 2019). The released fatty acids are converted by the mitochondria of hepatocytes in the process of β-oxidation to acetyl-CoA. With low blood glucose levels during the Krebs cycle, the accumulated acetyl-CoA is used to produce ketone bodies. The three main ketone bodies are acetoacetate (AcAc), b-hydroxybutyrate (BHB) and acetone. The first two are the most important to produce energy for the body. Due to its volatile nature, acetone is eliminated through the lungs and through the kidneys. AcAc and BHB in the mitochondria of tissues other than liver tissues are converted into ATP in the Krebs cycle (Glew, 2010).

The ketogenic diet is a very demanding diet in many ways. It must be strictly respected not only by the sick person, but also by their caregiver. It often promotes caloric reduction, which can lead, along with elimination, to nutritional deficiencies and malnutrition. It should be remembered that not all the products allowed in it are generally considered healthy. The most common sources of fat in KD are oils, fatty meats and fish, fatty dairy products, including cream and cheese, and eggs. Additionally, the diet should be enriched with low-starch vegetables. There are special nutritional preparations available on the market that ensure the optimal composition of the diet and better control over ketosis (Freeman, 2010). The use of a ketogenic diet in the treatment of cancer depends on the type of cancer, its subtype, location, and genetic factors (Pondel, 2020). The studies carried out on both the animal and human models seem to be contradictory.

SEARCH STARTEGY AND SELECTION CRITERIA

The review contains all studies from 2007 to 2021 listed in PubMed for the search terms: ketogenic diet, diet, low-carbohydrate diet, cancer, glioblastoma, glioma. In the studies, the parameters relevant to the review were first and foremost, survival, tumor size, side effects, and group size. 12 studies on an animal model and 9 studies on a human model were selected. 3 case studies were also taken into account.

ANIMAL MODEL RESEARCH

Studies in animal models often show positive results. However, their result depends on many factors, which makes it even more difficult to decide whether KD therapy is effective and should be recommended in the treatment of GBM.

Nutritional ketosis is often used as an adjunct to conventional treatment. Abdelwahab et al. studied mice with GL-261 malignant glioma. Both in the group of animals undergoing radiotherapy and chemotherapy (temozolamide), their lives were prolonged during the use of KD compared to the control group (Abdelwahab 2012; Abdelwahab, 2011). Also, studies from 2014 showed that only a combination of diet and chemotherapy is an effective method to extend the life of sick animals. Without treatment, this effect was not observed for the KD group (Rieger, 2014). Another study also found that KD combined with caloric restriction, chemotherapy or a hyperbaric chamber increased survival. This has not been observed in the no-treatment group on either a ketogenic or calorie restricted diet (Augur, 2018). Similar results were obtained in another study where mice with malignant glioma on a low-calorie ketogenic diet were given 6-diazo-5-oxo-L-norleucine. In this group, tumor growth was inhibited and survival increased. No such correlations were observed in the control group on a standard diet treated with 6-diazo-5-oxo-L-norleucine. In this study there was no caloric deficit control group without Kd and treated with 6-diazo-5-oxo-L-norleucine, therefore we cannot exclude that caloric restriction and treatment are the most important factor (Mukherjee, 2019).

There are reports in animal studies relating to the successful use of KD in the treatment of GBM without chemotherapy or radiotherapy. This is confirmed by a study on mice that used the 8: 1 ketogenic diet. In this diet, the glucose level did not change, but the level of ketone bodies increased significantly, which resulted in a decrease of tumor progression, an increase of survival compared to the control group (Stafford, 2010; Scheck, 2012). The positive test results were explained by decrease ekspression of coding genes IGF-1, Ras GTPase activating protein (RasGAP) i mitogenactivated protein kinase 8 (MAPK8) in mause tumor. This resulted in changes in the signaling pathways of factors responsible for the growth of glioblastoma: IGF-1, platelet-derived growth factor (PDGF) and epidermal growth factor receptor (EGFR) (Scheck 2012). Similar results were also obtained by Lussier et al. using dietary intervention in mice with GL-261 malignant glioma. The anti-tumor effect was achieved in comparison with the control group (Lussier 2016). However, in another study, KD reduced microcir-culation of a malignant tumor in mice (Woolf, 2015). Also, positive results KD shows research with three group of mice. On a control, ketogenic, and low-carbohydrate, high-fat (HFLC) diet. The last two diets caused a decrease in glucose and an increase in ketone bodies which increased the survival rate of animals in these groups. This study indicates that the HFLC diet is an effective alternative to KD. This is crucial for post-treatment patients who refuse or are contraindicated in following a strict ketogenic diet for the rest of their lives. The results seem interesting, and this thesis should be examined more closely (Martuscello, 2015).

In opposition to these positive results, there are numerous studies that do not support the effect of the KD diet. In a study by Zhou et al. three interventions were used in mice bearing U87-MG glioblastoma. A ketogenic diet without caloric restrictions, a ketogenic diet with caloric restrictions and a standard diet. Tumor growth was inhibited and the survival rate increased only in the group of mice with ketosis and caloric deficit. This would indicate that reducing the daily caloric intake along with ketosis is the only effective method. There was no caloric deficit-only group in this study, which does not explain the results of the study (Zhou, 2007). A 2016 study, however, where two groups of sick mice on a caloric-deficient diet were compared, and one of them was additionally put

into ketosis, no differences were found between them. The effect was neither recorded in terms of survival nor tumor growth inhibition was observed, although both the glucose levels in the subjects were low and the ketone levels were high (De Feyter, 2016). A study on mice on a ketogenic diet and those in the control group should also be cited. Both groups had statistically similar results in terms of survival and tumor growth (Maurer, 2011).

HUMAN MODEL RESEARCH

The results of human studies appear to be highly debatable. The type of diet (caloric restriction, amount of carbohydrates), the duration of the intervention, the number of patients who completed the study compared to the initial group, and the results (tumor growth, survival, quality of life, dietary side effects) should be taken into consideration.

The 2014 research was started by 20 patients and 8 completed. Patients with standard treatment were put on a ketogenic diet containing plant oils, without caloric restriction. Among 8 patients with stable ketosis, life was prolonged without tumor progression, however, it should be remembered that the study only lasted 6 weeks. Patients reported improved quality of life on a ketogenic diet. The authors concluded that the KD diet was unsuccessful when used without standard treatment (Rieger, 2014). Similar results were obtained by Champ et al. in patients after tumor resection, radiotherapy and the KD diet. The tumor did not recur within 9 months (Champ, 2014). Mention should be made of another study using perillyl alcohol (POH) and a ketogenic diet in patients with recurrent glioma. The survey completed 9 of 17 participants. After three months of treatment, partial response was observed in 77.8% of patients, stable disease in 11.1% and progressive disease in 11.1%. Compared to the control group (standard diet, n = 8), partial response was 25%, stable disease 25% and PD 50% (Santos, 2018). Strowd et al. used a modified Atkins diet (20g of carbohydrates per day) in 8 patients for 2-24 months did not achieve a significant extension of life compared to the expected. The only advantage of nutritional ketosis was the reduction of epileptic seizures among patients (Strowd, 2015). In a study by Martin-Mc Gill et al. after 3 months of KD intervention (20 grams of carbohydrates per day) and standard therapy, patients' weight decreased but their quality of life improved according to subjective judgment (Martin-Mc Gill, 2018). In a study by Martin-Mc Gill et al. in 2020, a ketogenic or ketogenic diet with MCT was introduced in 12 people diagnosed with glioblastoma. Only 4 people completed the three-month intervention, including one at MCTKD. Global Health Status (GHS) improved in patients after KD and decreased in patients after MCTKD (Martin-Mc Gill, 2020). In these studies, we know nothing about tumor progression and survival. Patients on the KD diet and standard treatment after 3 months saw a reduction in BMI, fatigue and the number of epileptic seizures, increased energy levels, physical mobility, and improved mood and cognitive functions. However, no information was provided on tumor progression (Panhans 2020). Latest research on 50 patients who were divided into two groups where re-irradiation combined with either SD (standard diet) or KD-IF (calorie-restricted ketogenic diet and intermittent fasting), 3 days of ketogenic diet (KD: 21-23 kcal/kg/d, carbohydrate intake limited to 50 g/d), followed by 3 days of fasting and again 3 days of KD. After one month, 20 patients who completed the study found that cognitive function had changed, such as progression-free survival (PFS) and overall survival (OS) with significant differences and Quality of Life unchanged (Voss, 2021). Among patients who did not receive standard treatment, only caloric reduction and nutritional ketosis did not show positive changes after 3 months. During this time, the tumor increased in size and the patient's body weight decreased (Shwartz, 2015).

CASE STUDY

In a study on a patient with glioblastoma after standard therapy, a ketogenic diet and caloric restrictions were applied. There was a 20% loss in body weight, but the final BMI was normal (20 kg/m^2). During 5 months of caloric restriction and 2 weeks of nutritional ketosis, the results of tomography did not show an increase in tumor volume, however, 10 weeks after discontinuation of diet, the tumor began to grow back (Zuccoli, 2010).

A patient with growing GBM IDH1 glioma refused standard treatment in addition to tumor resection. Before and after the procedure, she used KD. After the procedure, slow tumor

growth was noted, but the patient's survival time without chemotherapy and radiotherapy was 80 months at the time of publication of the case study (Seyfried, 2021).

In another study on a 38-year-old man diagnosed with glioblastoma, apart from a ketogenic diet, standard therapies (resection, chemo-radiotherapy), vitamin and mineral supplementation, treatments in a hyperbaric chamber and numerous additional medications were also used. After 9 months, the seizures weakened and the tumor shrinked. However, the authors cannot determine which intervention brought the best results (Elsakka 2018).

DISCUSSION

The results of human studies appear to be inconclusive. The research is completed by a small percentage of patients, which makes the analysis even more difficult. This is due to the lack of effects, poor diet tolerance, or complications that may be associated with it. In many studies there is no control group, dietary assumptions often differ, and the state of ketosis results in a reduction in calories, which may also influence the development of the disease. Many study authors admit that KD intervention without standard treatment is usually of no avail. It should be noted that scientists emphasize that the best results of the KD diet occur when combined with other therapeutic methods such as tumor resection, chemotherapy, radiotherapy, vitamin and mineral supplementation, treatments in a hyperbaric chamber or additional drug support (Elsakka, 2018). The benefits of KD in cancer and glioblastoma are very important. One of them is reducing the tumor, stopping its growth, and thus increasing the survival time (Rieger, 2014; Champ, 2014; Santos, 2018). Other patient reported benefits include a reduction in fatigue and epileptic seizure frequency (Strowd, 2015; Martin-Mc Gill, 2018, Panhans, 2020). Despite many positive reports, one cannot forget about the problems and threats that KD brings. During nutritional ketosis, reported side effects were hypoglycaemia, hypernatraemia, hypocalcaemia, gastrointestinal complaints (diarrhea, nausea, vomiting, dyspepsia), and dry mouth (Martin, 2020). Enother side effects of the ketogenic diet is "keto-flu". It occurs during the first week of diet as the body adapts to the new composition of nutrients. It manifests with gastrointestinal symptoms, headache and muscle cramps which are results of a loss of fluid and electrolytes as well as metabolic acidosis (Bostock, 2020). All these negative aspects mean that few people are able to stick to the ketogenic diet. In a study by Kossoff et al. the diet was started by 30 adult patients with incurable epilepsy who were treated with the Atkins diet variant (15 g of carbohydrates/day). After a month, there were 26, after 3 months, 20, 6 months lasted 14. People who stopped the diet reported lack of effectiveness (9 people), 6 considered the diet difficult to implement, and one 1 did not start the diet despite registration (Kossoff, 2008). In another study, patients who gave up on diets indicated reasons such as "too restrictive", "inconvenient" (Panhans, 2020).

Caloric restrictions in dietary intervention often occur unintentionally due to decreased appetite on a high-fat diet (Pondel, 2020). In studies, the caloric deficit itself is often a factor supporting the treatment of glioblastoma (Zuccoli, 2010). It remains to be considered whether the factor affecting the health of patients with glioblastoma during the intervention is dietary ketosis, a caloric deficit, or a combination of both? The caloric deficit is often a disadvantage in patients who are of normal weight or are already in the state of cancer cachexia. It is known that malnutrition is a very common cause of death among cancer patients. Cancer cachexia is characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. It negatively affects quality of life, physical, emotional and social well-being and responsiveness to chemotherapy. Adequate nutritional support remains a mainstay of cachexia therapy (Baracos, 2018; Sadeghi, 2018).

The long-term effects of LCH diets are still unknown. It is known that due to the predominance of saturated fatty acids, it may worsen the results of the lipid profile (increase in LDL, VLDL, non-HDL fractions) and promote cardiovascular diseases (Pondel 2020). In research by Rosenbaum et al. the KD was associated with increased cholesterol and inflammatory markers after 4 weeks (Rosenbaum, 2019) (O'Neil, 2020). Due to the elimination of numerous products on the KD diet, possible deficiencies may occur. It is recommended to enrich the ketogenic diet with supplementation of water-soluble vitamins such as: vitamin B_1, B_2, B_6, niacin, folic acid, biotin, pantothenic acid, zinc, selenium, calcium, carnitine and omega-3 acids (Pondel, 2020). Most of these ingredients which

may be deficient during the KD diet actively support the immune system in anti-cancer immune responsiveness (Soldati, 2018). The diet that, according to many studies, shows the most effective anti-cancer properties is the Mediterranean diet. It is rich in products such as whole grains (about 50-60% of the total caloric intake), vegetables, fruit and legumes, which are mostly not allowed on ketogenic diet. In the long term, the lack of these products and the ingredients they contain may paradoxically contribute to cancer recurrence (Divella, 2020). Lack of consumption of the right amount of fiber and prebiotics may adversely affect the condition of the microflora of patients during the KD diet, at the same time favoring inflammatory and neoplastic processes (Soldati, 2018). Medicine still needs to search for new therapeutic combinations that include dietary metabolic regulation with conventional therapies. Perhaps this will avoid the side effects of long-term chemotherapy or multiple irradiations. (Strowd, 2015).

CONCLUSION

Despite numerous studies related to the ketogenic diet in the treatment of cancer, inclu-ing glioblastoma, there is still no clear position. There are more and more questions that need to be answered before KD is proposed as one of the treatments for cancer. The contraindications for the use of KD or the criteria for when the diet should be discontinued should be clearly defined. This could be too low body weight, hypoglycaemia or gastrointestinal side effects. It is worth defining a dietary management schedule if it is decided to be used one of the LCH diets. Uniform recommendations must be made for the diet to be most effective while minimizing side effects. Accurate education of patients who choose this type of therapy is essential. The first time of adaptation to KD should take place in the hospital ward so that the impact of "keto-flu" or other side effects on the patient's well-being can be minimized.

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