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REVIEW

METABOLIC PERSPECTIVE OF CANCER: KETOGENIC DIET AND METABOLISM ANTAGONISTS

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ABSTRACT

Abnormal cancer metabolism, a trending topic in recent years, has given rise to various studies and promising results for some cancer types. Ketogenic diets with metabolism antagonists, hyperbaric oxygen, and hyperthermia constitute part of the treatment options that were derived from the metabolic perspective of cancer. Most of them exploit the glucose, glutamine, and fermentation dependence of cancer cells. In addition, they are known to increase the efficacy of current therapies. Ketogenic diet aims to decrease available glucose and increase non-fermentable ketone bodies. In this review, we aim to inspect the abnormal cancer metabolism, starting with the Warburg effect, current advancements, and promising therapeutic uses of these metabolic pathways by primarily focusing on the ketogenic diet and metabolism antagonists.

Keywords: Cancer, glucose, ketogenic diet

INTRODUCTION

Cancer presents a major public health threat worldwide and is known to be the second leading cause of death in the United States of America (USA). Approximately 600.000 people died per year due to cancer between 2015 and 2020 in the USA, and it is estimated that 609.000 people will die from cancer in 2023 despite the efforts made by states, healthcare industry, and non-governmental organizations (1, 2). The majority of these deaths are predicted to result from cancers of the lung, prostate, and colorectum in men, whereas lung, breast, and colorectal cancers are the leading causes in women (1). The primary risk factor for lung cancer is tobacco use, which has been known for many years (3). We have been getting promising results for the treatment of cancer types including but not limited to breast, thyroid, and prostate. However, we cannot say the same for glioblastoma multiforme (GBM) or lung cancer (1, 4). Even though a remarkable effort was put in to improve the prognosis of these groups of cancers, significant outcomes have not yet been seen. It is understood that current treatment modalities need revisions and improvements. These updates should be made to acknowledge the importance of the pathological metabolic processes seen in cancer cells, which have been known since the 1920s but have not been utilized enough in treatment approaches (5).

Even though the first observations of metabolic abnormalities in cancer cells were made almost a century ago, they have not been the focal point of cancer treatment research (5). Utilizing one of the hallmarks of cancer, the abnormal metabolism, in treatment approaches is only a recent focus of researchers and is still debated (6-8). We have seen a massive surge in published papers about this topic in recent years (9).

For many years, abnormalities in cancer metabolism have been used for prognosis prediction and diagnosis in an orthodox paradigm via fluorodeoxyglucose-positron emission tomography (PET). Excessive glucose dependence of tumors is utilized in PET (8). Developing a metabolic perspective suggests the use of this metabolic abnormality not only for diagnosis and prognosis but also for treatment strategies that can be combined with current therapies (7, 8). In this review, we aim to explore the unique and altered metabolism of cancer cells and how it can be utilized primarily via the ketogenic diet. We will also mention some therapy options that can be combined with ketogenic diet therapy.

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Cancer Metabolism

Studies revealed the consequences of abnormal metabolism of cancer at various stages of tumorigenesis. Some changes, such as the modification of metabolite influx and reprogramming of the assignment of nutrients to metabolic pathways, are seen to meet the bioenergetic, biosynthetic, and redox demands of cancer cells. Also, alterations of the tumor microenvironment components and differentiation of cancer cells create long-ranging effects on cellular fate. Reprogrammed metabolism is considered a hallmark of cancer because some of the metabolic changes are observed across various types of cancer (5, 10).

With increased energy usage by cancer cells due to reasons such as increased proliferation, cells must increase nutrient uptake. Two major nutrients that mammalian cells use to support biosynthesis and survival are glucose and glutamine (5). Cells use glucose and glutamine not only as energy sources but also as carbon sources since the catabolism of these monomers produces a variety of carbon intermediates for biosynthesis.

1. Glucose uptake

In the 1920s, Warburg et al. (11), who were working on the metabolism of tumors, described the increased glucose consumption by tumorous cells compared to normal cells. Further studies showed that increased glucose consumption correlates with a poor prognosis of cancer (12, 13). Cancer cells must increase their glucose uptake to match this increased glucose consumption. In mammalian cells, glucose uptake occurs via the glucose transporter (GLUT) family of membrane proteins. In many types of cancer, upregulation of GLUT1 and GLUT3 meets an increased need for glucose (14-16). Based on previous research, an increase in GLUT expression seems relevant to neoplastic transformation. However, another interpretation suggests that increased GLUT expression is caused by decreased intracellular glucose levels (17).

Various mechanisms regulate GLUTs. A study showed that hypoxia-inducible factor-1 (HIF-1) increases the expression of GLUT1 in hypoxic conditions, which is an important regulatory mechanism because of the presence of hypoxic areas in a tumor, described as tumor hypoxia (18). Hyperbaric oxygen therapy (HBOT) can decrease the expression of HIF-1 and reverse the Warburg effect in cancer cells, which is explained later in the text (19). Since various mechanisms regulate GLUT expressions, it is yet unknown whether HBOT directly affects GLUT expression. A study has shown that HBOT promotes GLUT4 expression in streptozotocin-induced type 2 diabetes mellitus mouse models (20). Further research is required to understand the association between HBOT and GLUT expression.

2. Warburg effect

The metabolic perspective of cancer utilizes the Warburg effect, which argues that, unlike normal cells, some cancer cells do not use the citric acid cycle and oxidative phosphorylation (OxPhos) for energy production. Instead, they predominantly use glycolysis followed by lactic acid fermentation to produce ATP even in the abundance of oxygen (11). This phenomenon, the Warburg effect, is also known as aerobic glycolysis (9). Glycolysis is ineffective in terms of the amount of ATP produced when compared to OxPhos, but it is 100 times faster than OxPhos. So, the exaggerated energy demand of rapidly proliferating cancer cells can be countered by an accelerated ATP-producing system. Also, this enhancement in the glycolysis pathway could provide sufficient NADH that is needed to sustain biosynthesis (7, 9). However, not all cancer cells fit into this perspective. Tumors are mostly heterogeneous, so there are Warburg-like and oxygen-consuming phenotypes (7).

3. Reactive oxygen species

The production of reactive oxygen species (ROS) naturally occurs with the reactions of oxygens via electrons. All reactive oxygen species types have unpaired valence electrons and unstable bonds. It has been known for years that reactive oxygen species damage all types of cells because of their highly reactive and unstable status. However, recent research has shown that ROS' implications can extend beyond their damage. While chronic and high-degree exposure to ROS can damage nucleic acids, lipids, and proteins, low to intermediate amounts of ROS can play a significant role in cell signaling cascades, even promoting cell survival (21, 22).

According to a research, OxPhos disruption leads to carcinogenic ROS accumulation (23). Genomic instability and mutations in cancer cells can be a downstream effect of ROS production (24). ROS can be thought of as a double-edged sword. Increased or tumor-promoting ROS can increase cell proliferation, cell cycle progression, survival signaling, genomic instability, epithelial-mesenchymal transition, and motility. If this threshold is exceeded, fatal effects are seen even on cancer cells. Cell cycle arrest, cell senescence, and cell deaths emerge secondary to excessive ROS levels, which are targeted by chemotherapeutics (22). Recent research has shown that injection of mitochondria isolated from healthy mouse livers into melanoma mouse models with lung metastasis has increased ROS levels compared to the control tumor group. This increase is more prominent in mitochondria isolated from young mouse liver rather than from aged mouse liver. Mitochondria replacement increased the survival days of the melanoma mouse models and delayed the growth of their tumors. In addition to these, it reduced glycolysis and reversed the Warburg effect (25). This paper shows that prophylactic treatment and acute treatment should be different in terms of ROS. ROS itself can both promote and inhibit carcinogenesis. More importantly, mitochondrial function and the Warburg effect are valuable for cancer prognosis.

Ketogenic Diet

Dietary regimens and fasting have been used for more than 2000 years to treat epilepsy. The ketogenic diet is one that had been used in the 1920s, but with the development of antiepileptic drugs, it has fallen into disrepute (26). Researchers have recently started to pay attention to the ketogenic diet in terms of efficacy, safety, mechanism of action, therapeutic

actions, and its potential effect on chronic diseases such as diabetes and cancer (27). In terms of cancer management, different studies revealed that ketogenic diet reduced tumor growth and improved survival in animal models with malignant glioma, colon cancer, gastric cancer, and prostate cancer (28).

There are many types of ketogenic diets including the mediumchain triglyceride ketogenic diet and the modified Atkins diet. Generally, ketogenic diets are characterized by their low carbohydrate (20-50 g) content, which approximately composes 5-10% of the total daily calorie consumption. Fat becomes the major calorie source. Ketone bodies are synthesized when carbohydrate sources are limited. Ketone bodies are organic compounds that are mostly derived from the free fatty acid breakdown process in the liver. Ketogenesis is also seen in the heart, brain, gut, and kidneys to some extent. Free fatty acids released from adipose tissue that enter the mitochondria of hepatocytes are used to form acetyl-CoA by β-oxidation. If glucose levels are high, acetyl-CoA is further oxidized through the tricarboxylic acid cycle and electron transport chain. If glucose levels are low, ketogenic enzymes such as thiolase and hydroxymethylglutaryl-CoA synthase contribute to the production of acetoacetate, β-hydroxybutyrate (BHB), and acetone, which are the main ketone bodies (29).

Insulin and glucagon are key regulators of ketogenesis. While glucagon stimulates ketone body synthesis, insulin inhibits this process via the inhibition of hormone-sensitive lipase, which is responsible for the release of free fatty acids from adipocytes, thus withdrawing the substrate from ketone body enzymes (30).

Some studies suggest that a ketogenic diet can facilitate cancer cachexia by lowering the blood glucose level. However, there are papers contrasting this view, showing that a ketogenic diet can mitigate cachexia. These incoherent results likely occur due to the absence of standardization of the ketogenic diet composition, length of treatment, number of consumed calories, and to what extent nutritional ketosis is achieved (31). Also, deficiency of micronutrients is documented in ketogenic diets in some cases (32). In addition, the use of a ketogenic diet in refractory epilepsy cases can negatively affect the developing skeleton. Medicalization and control are important for the therapeutic use of a ketogenic diet to avoid its potential side effects (33). The most reported symptoms are constipation and asthenia. Hypoglycemia is the most anticipated adverse effect; however, mild hypoglycemia can be intended for therapeutic interventions (34). Because cancer cells lack metabolic flexibility due to their mitochondrial mutations and abnormalities, this hypoglycemic state can aggravate oxidative cellular stress. However, healthy cells in the same situation can compensate for the lack of glucose via ketone bodies. Mild hypoglycemia can also reverse the Warburg effect by reducing the amount of glucose (35).

Glucose transporter overexpression is associated with carcinogenesis. One study shows that a calorie-restricted ketogenic diet (KD-R) can promote GLUT expression, and this expression is likely to arise from the hypoglycemia caused by the KD-R (36).

Both ketogenic diets and insulin-like growth factor (IGF-1) reduce blood glucose levels. As IGF-1 is a biomarker of tumor progression and angiogenesis, circulating amounts are important. It is shown that the decrease in blood glucose levels is almost equal to the decrease in IGF-1 when brain tumor mouse models are put on a ketogenic diet (37).

Being aware of the glucose and fermentation dependence of cancer cells can offer some therapeutic interventions. There is a growing interest in the literature on ketogenic diet use both *in vitro* and *in vivo* (38). The main point is to make glucose-dependent cancer cells starve using their inability to entirely utilize the non-fermentable ketone, in contrast to the healthy cells that can (23, 38).

As mentioned above, while some types of cancer depend on aerobic glucose fermentation, the same phenomenon may not be valid for other cell lines and cancers. Therefore, the success of ketogenic diet therapy may vary depending on the different properties of cells since tumors are mostly heterogeneous (7).

Expression of ketolytic enzymes can provide predictive information about the response of a tumor to ketogenic diet regimens. An *in vitro* experiment showed that BHB supplementation to hypoglycemic groups PANC-1 cell line does not affect their proliferation, whereas BHB supplementation significantly promotes cell proliferation in HeLa cells. When researchers intentionally knocked down ketolytic enzymes 3-hydroxybutyrate dehydrogenase 1 (BDH1) and succinyl-CoA:3-oxoacid CoA transferase 1 (OXCT1) by infecting HeLa cells with lentivirus, BHB supplementation stopped promoting proliferation. In addition, mouse models of the PANC-1 cell line showed that mice fed a ketogenic diet had decreased tumor volume and weight and an increased percentage of survival when compared to mice in an approximately isocaloric standard diet group. HeLa mouse models showed that mice put on a ketogenic diet had a decreased survival rate. In mouse models including BDH1 and OXCT1, the knockdown of HeLa cells showed that mice fed a ketogenic diet had less tumor volume and weight when compared to the standard diet group. Interestingly, BHB supplementation in a high glucose medium did not affect the proliferation of HeLa cells *in vitro* (39).

In order to sustain ROS levels in tumor-promoting space, some antioxidant biomolecules, such as glutathione, can be required in the tumor. As the production of glutathione requires glycolysis and pentose phosphate pathways, which need glucose, a ketogenic diet can promise some treatments by limiting the availability of glucose (23-25, 38).

Also, it was shown that a ketogenic diet can be used to sensitize cancer cells to both radiotherapy and chemotherapy (38). This is the reason why researchers are investigating whether a ketogenic diet can be combined with current therapies.

The first case report of confirmed GBM treatment consisting of standard therapy (radiation with temozolomide chemotherapy)

with the combination of a ketogenic diet has shown rapid unusual regression of GBM (40). The relatively positive outcome of the ketogenic diet is attributed to its role in preventing high blood glucose levels, which promotes angiogenesis and prevents apoptosis via GF-1/phosphoinositide-3-kinase (PI3K)/Akt/HIF-1α signaling pathways (37, 41). Also, a decrease in inflammatory status is likely to occur via a ketogenic diet. The paper also notes that ketone bodies can be considered alternative metabolic fuels that can be utilized by healthy cells but not by cancer cells because of their mitochondrial dysfunctionality.

One case report that presents a human epidermal growth factor receptor 2 negative breast cancer that metastasized to the lungs, brain, mediastinum, liver, abdomen, and bones includes ketogenic diet use as well as hyperbaric oxygen and hyperthermia (HT) in combination with standard chemotherapy treatment. HT has a direct cytotoxic effect against cancer cells by increasing the treated tissue temperature up to 42 °C or higher and therefore exploiting the heat sensitivity of cancer cells. HT may also sensitize cancer cells to radiotherapy and chemotherapy, thus increasing their efficacy (42). It inhibits DNA repair and causes DNA damage by promoting ROS production (43). Hyperbaric oxygen therapy is applied by administration of 100% oxygen at a higher pressure than 1 atmosphere. In cancer treatment, HBOT aims to fight against the cancer-promoting effects of tumor hypoxia by increasing blood oxygen levels (20). Hyperbaric oxygen is known to work synergistically with radiation therapy and some chemotherapeutic agents (43). In addition, hyperbaric oxygen adds to the positive effect of ketogenic diets on the mean survival time of mice with systemic metastatic cancer. However, hyperbaric oxygen is not efficient on its own (44). Hyperbaric oxygen can also promote ROS production (45). Both hyperthermia and hyperbaric oxygen can synergistically work with prooxidant chemotherapy regimens. A ketogenic diet can compensate for this prooxidant status via its antioxidant effects on healthy cells, and it can also promote ROS production in cancer cells (46, 47).

Metabolism Antagonists

To target and prevent glycolysis and glutaminolysis in cancer cells, there are some molecules, including 2-deoxy-D-glucose (2-DG), which is a non-metabolizable glucose analog, and 6-diazo-5-oxo-L-norleucine (DON). These metabolism antagonists can be combined with a kind of ketogenic diet regimen, thus utilizing the synergistic effect and strengthening the standard therapy (48, 49).

Aerobic glycolysis is preferred by cancer cells due to its potential advantages. In order to sustain glycolysis, cancer cells can increase their glucose uptake 20-30 times compared to normal cells. This increased uptake requires the overexpression of GLUT (50). 2-DG radioisotope analogs are used to detect transformed, malignant cells by exploiting this glucose uptake characteristic (8). 2-DG itself competes with glucose and competitively inhibits its uptake. After entering the cell, 2-DG is phosphorylated by hexokinase II to form 2-deoxy-D-glucose-6-phosphate. However, it cannot be metabolized further and gets accumulated in the cell, where it allosterically inhibits hexokinase activity. Cell growth inhibition, arrest in the cell cycle, and eventually cellular death are seen (51). There are ongoing studies *in vivo* and *in vitro* investigating the potential use of 2-DG and its derivative, aiming to have more drug-like properties for use in combined anticancer therapies (52-54).

Even though DON has been studied for more than 60 years, it was abandoned in clinical trials because of its nausea and vomiting side effects. However, it is important to note that, in that period, acceptable side effect criteria were stricter. Most of the current chemotherapeutic agents cause similar side effects in patients. As a potent glutamine antagonist, it can be reclaimed as a DON prodrug with improved therapeutic index and side effects (55, 56). Sirpiglenastat is one of the DON prodrugs with a better therapeutic index, and it is being evaluated in phase I/IIa clinical trials (57).

Glioblastoma multiforme cells are dependent on glutamine as well as glucose. In addition, glucose deprivation, which can be achieved by a ketogenic diet, directs cells to use glutamine even more. Glutamine metabolism is significant in rapidly proliferating tissues to produce biomolecules (58). Therefore, the use of DON in the treatment of GBM has been considered. An *in vivo* study has used DON with a calorie-KD-R to target both glutaminolysis and glycolysis in GBM mouse models. KD-R-positive DON reduced cell proliferation. Synergistically, KD-R facilitated the delivery of DON to brain tissue. Furthermore, since cancers are heterogeneous, detection of glutamine dependence is sensible (59). As DON can cause significant side effects, better tolerability can be achieved with improved delivery methods, thus lowering the therapeutic doses (56).

When metabolic therapies are compared with chemotherapeutics in terms of drug delivery systems, derivatives, and similarity of side effects, metabolism antagonists are more appealing.

Press-pulse Strategy

Exploitable abnormal cancer cell metabolism offers a variety of therapeutic interventions, including a ketogenic diet, hyperbaric oxygen therapy, glucose, and glutamine antagonists. The use of these interventions in a systemic way is described as a "press-pulse strategy". Press disturbance describes the chronic stress induced by a calorie-restricted, isocaloric ketogenic diet. Pulse disturbance describes the acute stress caused by glucose-glutamine antagonists and hyperbaric oxygen therapy (35). Some clinicians also include HT in the pulse disturbance category (42, 43). Due to the abnormal metabolism mentioned in the review, these stress factors can boost the efficacy of standard therapies for particular types of cancer, such as chemoradiotherapy (Figure 1). These cost-effective, non-toxic, and encouraging therapies could be effective additions to standard therapy in the future of oncology.

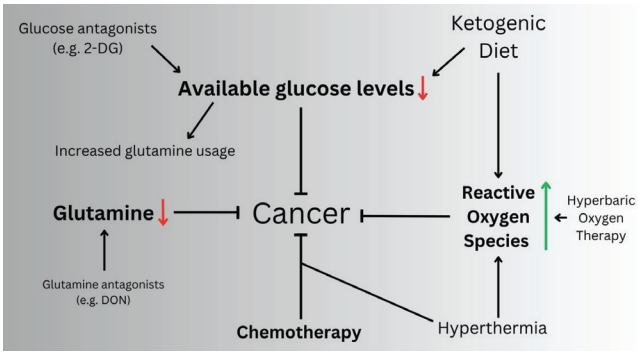

Figure 1: Schematic explanation of therapies exploiting abnormal cancer metabolism. Green arrows indicate an increase and red arrows indicate a decrease.

2-DG: 2-deoxy-D-glucose, DON: 6-diazo-5-oxo-L-norleucine

CONCLUSION

Cancer has been interpreted as a genetic disease for years. Studies, as well as treatment modalities, are conducted in line with this paradigm. This paradigm has made the field of oncology successful to some extent; however, for some cancer types, satisfying results have not been achieved. The abnormal metabolism of cancer cells, which was described by Warburg et al. (11) in the 1920s, has gained popularity in recent years to take oncology one step further. This metabolic perspective and its promising treatment options exploit the lack of metabolic flexibility in cancer cells. Therapeutic approaches centered on this aspect of tumor cells are mostly non-toxic and have anticancer properties. Furthermore, they enhance the efficacy of current therapies, thus making them more tolerable for patients due to their reducing effects on the minimum effective dose of chemotherapeutics. As lower doses of chemotherapeutics are given, chemotherapeutic resistance development decelerates.

One of the main targets of metabolic treatments is the glucose and fermentation dependence of cancer cells. The ketogenic diet, which is characterized by low carbohydrate and high lipid intake, exploits this status by reducing available glucose and increasing non-fermentable ketone bodies. Ketone bodies cannot be metabolized entirely by some cancer cells; however, normal cells can utilize them. Ketone bodies can also promote ROS production in cancer cells. However, there are common side effects of ketogenic diets, including constipation, asthenia, and hypoglycemia (34). HBOT and HT are other stressors for cancer cells that are known to work synergistically with a ketogenic diet. Also, there are studies investigating the use of metabolism antagonists such as 2-DG and DON. They compete with glucose and glutamine and prevent their metabolism (48, 49). These significant side effects are documented, so prescription and use require considerable attention. The press-pulse strategy describes the systematic combination of these metabolic stressors. Similar to how some chemotherapeutics may not be effective in some cases, the ketogenic diet and other metabolic therapies may not show anticancer properties unilaterally as well. Therefore, personalized medicine in cancer treatments is likely to play a major role not only in current therapies but also in metabolic therapies. As a result, the metabolic perspective of cancer is a rising topic in oncology. The emerging literature and evidence suggest that the use of metabolic treatment strategies, both separately and in combination with current therapies, will be beneficial.

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