



Possible Nutrition-Related Mechanisms of Metabolic Management in Cancer Treatment

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Received 2020 July 19; Revised 2020 October 26; Accepted 2020 October 26.

Abstract

Context: Somatic mutation theory has been considered as a potential cause for cancer. However, major inconsistencies with the gene theory have necessitated serious reconsideration of this assumption. According to these inconsistencies, cancer may be considered as a metabolic disorder. According to the mitochondrial metabolic theory, substrate-level phosphorylation has been suggested to be superior to oxidative phosphorylation in cancer cells. Cancer metabolic therapies such as ketogenic diets (KD) and limitation in glutamine and calorie can be beneficial and are in line with this theory. In this study, we have reviewed the potential effects of KD as well as glutamine and calorie restriction in various types/stages of cancer with a focus on possible mechanisms.

Evidence Acquisition: A comprehensive electronic search of different databases was performed using “cancer”, “ketogenic diet”, and “metabolic” as the main keywords. A comprehensive electronic search of different databases was performed using “cancer”, “ketogenic diet”, and “metabolic” as the main keywords.

Results: Emerging evidence has indicated that KD can affect tumor cells by reducing glucose availability and simultaneous elevation of ketone bodies as non-fermentable metabolic fuels. KD has been suggested to be more effective as a non-toxic therapeutic measure in combination with glutamine targeting agents, chloroquine for lysosomal targeting, hyperbaric oxygen therapy, and calorie restriction.

Conclusions: This metabolic approach can be considered as a promising non-toxic strategy for cancer management.

Keywords: Cancer, Ketogenic Diet, Glycolysis, Glucose, Glutamine, Non-Toxic, Metabolic, Hyperbaric Oxygenation

1. Context

Many of the current cancer treatments have considered cancer as a genetic disorder. However, major inconsistencies with the gene theory have necessitated serious reconsideration of this assumption. For instance, the absence of gene and chromosomal mutations in some cancers that reinforce the somatic mutation theory (1-4); driver gene mutations in various normal human tissues including the breast (5-7); and lack of various cancers in chimpanzees despite the large similarity in gene sequence with humans are some pieces of evidence indicating this inconsistency (8-10). Moreover, nuclear/cytoplasm transfer experiments have shown the possibility of normal cell and tissue production from tumorigenic nuclei relocated in normal mitochondria containing cytoplasm (11). Recent reports have shown that multiple oncogenic

pathways and growth behavior can be down-regulated in metastatic breast cancer cells by normal mitochondria (12, 13). These findings indicate that normal mitochondrial function plays a vital role in suppressing tumorigenesis regardless of the tumor nucleus gene or chromosomal abnormalities. These findings also suggest that the nuclear genome mutations are not the primary cause of cancer. Cancer was suggested as a metabolic disease that is caused by an irreversible damage to cellular respiration. Cancer cells heavily depend on glucose fermentation to lactate for their metabolic demands even under sufficient oxygen supply (14). The glucose transporter molecules on tumor cell surfaces have shown a substantial up-regulation. Also, some glycolytic enzymes including hexokinase 2, lactate dehydrogenase-A, phosphofructokinase, and pyruvate kinase-M2 have been reported to be overexpressed. Abnormal function of the tricarboxylic acid (TCA) cycle enzymes

in cancer cells cause a remarkable reduction in ATP production via decreased oxidative phosphorylation and enhanced glycolysis (15, 16). The secretion of lactic acid increases during increased glycolysis and can decrease the extracellular pH around the tumor. This acidosis induces normal cell death, enhances angiogenesis, deteriorates extracellular matrix, and suppresses tumor antigen-specific immune responses which promote metastasis. Consequently, the tumors become more aggressive and desmoplastic (17). Also, glycolysis generates NADPH via its pentose phosphate pathway offshoot, which produces glutathione that decreases reactive oxygen species-induced death in cancer cells (18). Also, carbon chains in cancer cells are used as precursors to produce essential cell proliferation materials including nucleic acids, proteins, and lipids (19). In light of these findings, cancer is a chronic systemic disease with a strong metabolic peculiarity that theoretically provides an ideal target for metabolic therapies.

Several examples of metabolic therapeutic strategies for cancer treatment are presented in this review study. This article has focused on the ketogenic diet (KD) and other metabolic therapies that increase the effectiveness of KD in metabolic treatment of cancer.

2. Evidence Acquisition

A comprehensive review of electronic databases including ISI web of knowledge, Scopus, PubMed, and Google Scholar using the main keywords of “cancer”, “ketogenic diet”, and “metabolic” was performed considering the published manuscripts until the end of June 2020. A manual search among the references of gathered articles was also performed to improve the precision of the review.

3. Results

3.1. Ketogenic Diet

Ketogenic diet high in fats and low in glucose, is an effective complementary and alternative therapeutic approach for managing a variety of human cancers. Since the number, structure, and function of the mitochondria and subsequently, oxidative phosphorylation in cancer cells are defective, the use of fatty acids and ketone bodies for ATP synthesis cannot be performed (20, 21). These diets lead to cell starvation and energy deprivation in cancer cells while normal cells can use either glucose or ketone bodies and survive. Besides, reduced levels of blood glucose decreases insulin and insulin-like growth factor (IGF) which are important players in cancer cell growth and proliferation (22). Decreased levels of glucose will also favors the reduction in substrates required in both glycolytic and

the pentose phosphate (PP) pathways which in turn leads to a decrease in cellular energy, and the synthesis of glutathione and nucleotide precursors.

Also it was demonstrated that under Ketogenic diets the hypoxic, acidotic, and glucose and glutamine enriched pro-tumorigenic microenvironment of tumor cells might become less inflamed (23-25). Ketogenic diets are associated with reduced cellular proliferation, impeded tumor growth, reduced inflammation, neovascularization and angiogenesis, and increased apoptosis (26). The underlying mechanisms have not yet been fully characterized. During tumor progression, many angiogenic activators such as interleukin 8 (IL-8), tumor necrosis factor α (TNF- α), hypoxia-inducible factors (HIFs), and vascular endothelial growth factors (VEGFs) support the process of angiogenesis. KD or caloric restriction in mouse glioma models disuade the formation of tumor microvasculature accompanied by a significant reduced levels of HIF-1 α and VEGF receptor. The anti-inflammatory effects of KD are performed by suppressing the activation of NLRP3 inflammasome and reduction of inflammatory factors like TNF- α , interleukin 1 (IL-1), interleukin 6 (IL-6), and interleukin 18 (IL-18), and prostaglandin E2 (PGE2).

Even at the epigenetic level, ketogenic diet and fatty acids inhibit Histone deacetylases (HDAC) enzyme and affect methylation (27, 28). RASSF1A as a tumor-suppressor gene has been reported to be epigenetically inactivated at high frequency in various cancer tissues. Also DNA-methylation of HIN1 gene promoter frequently occurs in breast cancer. Epigenetic silencing of HIN1 expression induces breast cancer cell growth, migration, and invasion. Any restoration in HIN1 expression due to the use of ketogenic diet can help to suppress cancer cells growth. The Ki-67 is a cell proliferation activity marker that correlates with the clinical course and prognosis of tumors. Obviously, the use of DNA methyltransferase inhibitors may represent a potential therapeutic strategy for breast cancer treatment. In totally, KD seems to promote its anti-proliferative effect on cancer cells by creating an unfavorable metabolic environment.

3.2. Clinical Studies

While, a large number of animal studies have provided evidence for anti-tumor effects of KDs (29), support for these effects is very limited in humans. Studies involving children or adults affected with cancer have demonstrated the safety and tolerability of ketogenic diets. These studies are also motivating clinical trial. To the best of our knowledge only 3 randomized controlled trials have been conducted on the anti-cancer effects of the ketogenic diet.

In our previous study we reported that chemotherapy combined with 12-week KDs might exert beneficial effects

by decreasing total body fat, TNF- α , and insulin as well as increasing IL-10. KD may lead to reductions in tumor size and down-staging in patients with breast cancer. KD can also improve the overall survival without any substantial side effects on the biochemical parameters and quality of life (30-32).

In another trial a significant between-group difference was reported in adjusted physical function scores, cravings for starchy foods and fast food, body fat and insulin between the patients with ovarian or endometrial cancer undergoing 12 weeks of KD and the control group (33, 34).

Also, compared to a standard diet (SD), low carbohydrate or ketogenic diets have been reported to improve the quality of life, physical performance, body composition, and metabolic health in patients with breast cancer (35).

These feasible and tolerable dietary approaches might improve the oncological outcomes and has the potential to improve the therapeutic response to medications that have been well documented in vitro and in vivo. However, further randomized clinical trials are needed to confirm these data.

3.3. Restricted Calorie

Restricted ketogenic diets can reduce glucose and elevate blood ketone bodies more effectively than calorie restriction or KD alone. Calorie restricted ketogenic diets induce both chronic and intermittent acute stress on the energy metabolism of tumor cell, while simultaneously protect and enhance the normal cell energy metabolism.

The favorable effects of fasting in chronic disease have been reported in several previous studies as reduced calorie intake provides protection against oxidative stress and aging in various organisms.

Fasting has been proposed to promote substantial changes in metabolic pathways and cellular processes including autophagy and stress response, as well as decreasing the IGF-1. As a result, other factors as Akt, Ras, and mTOR will be affected and will down-regulate cell growth and proliferation (36).

The anti-angiogenic, anti-inflammatory, and proapoptotic effects of fasting and dietary restriction target multiple cancer hallmarks (37-40) which enhances the efficacy of chemo- and radiation therapy and reduces the side effects. Hence, lower dosages of chemotherapeutic drugs can be used in adjuvant therapy with calorie restriction or ketogenic diets.

The existing data support the safety and feasibility of these approaches and suggest an improvement in the quality of life and fatigue of patients under chemotherapy (41, 42). In another randomized trial in 13 patients with breast cancer, demonstrated no significant differences in the toxicity resulted from chemotherapy in patients undergoing

fasting, while DNA damages on peripheral blood mononuclear cells were significantly reduced during the first 30 minutes after intervention in fasting patients (43). However, data regarding the effects of this approach on patient survival outcomes are still controversial and need to be considered more in future studies.

3.4. Targeting Glutamine for Metastatic Cancer

While glucose serve as a prime fuel for growth and development of various tumors, some tumors use glutamine (44-47). Glutamine targeting in glutamine-dependent cancer cells can be a novel potential therapeutic approach. Glutamine plays several important roles in various metabolic pathways. Its amide nitrogen is used for nucleotide synthesis. Also, the glutamine-derived glutamate is used in protein synthesis by providing anapleurotic carbons to the Krebs cycle through alpha-ketoglutarate (alpha-KG). It also participates in ATP synthesis through the TCA cycle (48). Tumor cells in hypoxic conditions can use the glutamine-derived ATP from the Krebs cycle. Excess glutamine can also promote cell growth and suppress autophagy through stimulating the activity of a cell signaling pathway called serine/threonine kinase mammalian target of rapamycin complex 1 (mTORC1) (49, 50).

Glutaminolysis is performed by glutaminase (GLS) which is upregulated in several cancers. The glutaminase inhibitor DON (6-diazo-5-oxo-L-norleucine) has shown clinical benefits (45, 51). It could be more effective in combination with glycolysis inhibitors and/or calorie restriction (52). DON has been shown to be effective in reducing both primary tumor size and systemic metastasis (53).

Since glutamine is involved in various cellular metabolic functions especially in the immune system, glutamine targeting must be more emphasized regarding its possible side effects than glucose targeting. As metastatic cells with characteristics of macrophages and other immune cells are more dependent on glutamine as a major fuel, then glutamine targeting should be an effective therapeutic strategy in reducing most metastatic cancers (54).

In addition, accumulating evidence suggests that glutamine metabolism is regulated by many factors including the origin, suppressor status, epigenetic alternations, and microenvironment of the tumor (55). These concerns should better be considered in developing dietary based glutamine targeting tumor therapy. The specific mechanisms mediating tumor cell adaptation to glutamine limitation also need to be defined (56).

3.5. Lysosomal Digestion

Phagocytosed glycoconjugates and proteins can undergo lysosomal digestion and generate glucose and glu-

tamine. It has been shown that glioblastoma cells with myeloid properties are able to survive in extracellular matrix material without any additive glucose and glutamine (57).

Cumulative concentration of lactate in the media was indicative of lysosomal digestion and aerobic fermentation of glycoconjugates in the extracellular matrix material. However, the glioblastoma cells died immediately after adding chloroquine that stops the lysosomal digestion (57). A similar mechanism has been reported in pancreatic ductal adenocarcinoma cells under low nutrient conditions (58). Hence, targeting the lysosomal digestion in low glucose and glutamine conditions can inhibit metastatic invasive tumors.

3.6. Ketogenic Diet in Combination with Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) has been demonstrated to enhance the ability of KD in reducing tumor proliferation and metastasis. Although the evidence from both animal and human studies support the anti-cancer effect of hyperbaric oxygen therapy (59). The effectiveness will be enhanced when it is combined with standard care prior to radiation therapy for glioblastoma multiform (60). However, the exact mechanism through which of hyperbaric oxygen affects the tumor is not clear yet. Hyperbaric oxygen has been suggested to reverse hypoxia and suppress tumor growth (61) and Hyperbaric oxygen therapy enhances oxidative stress and peroxidation of lipids in glioblastoma multiform cell membrane (62). Also, exogenous ketones can enhance the effects of the ketogenic diet and hyperbaric oxygen therapy (63).

Although hyperbaric oxygen and radiotherapy both induce oxidative stress and kill tumor cells, normal cells are more compatible with the former one.

Consistent with findings of previous case report studies (64, 65), a complete response has been reported with a 6-month combination of chemotherapy, ketogenic diet, hyperthermia, and hyperbaric oxygen therapy in a patient with breast cancer (66).

Thus, the combined use of KD along with other metabolic approaches and standard therapy in order to enhance the therapeutic response in cancer can be used to design clinical trials for non-toxic management of most cancers.

4. Conclusions

Glucose and glutamine restriction along with increasing the non-fermentable ketones can be a potential complementary strategy for cancer treatment. Also, targeting the lysosomal digestion through the administration of

chloroquine and hyperbaric oxygen combined with a ketogenic diet will kill tumor cells. Data from further prospective randomized trials are needed to confirm these data.

Acknowledgments

We would like to thank Clinical Research Development Center of Ghaem Hospital, Mashhad University of Medical Sciences, for their assistance in this manuscript.

Footnotes

Authors' Contribution: Adeleh Khodabakhshi and Hossein Davoodi did search. Adeleh Khodabakhshi wrote manuscript. Maryam Mahmoudi rewrote manuscript. Hassan Mehrad Majd did critical review.

Conflict of Interests: The authors declare that they have no conflict of interests.

Funding/Support: Not applicable.

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