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KETOGENIC DIET AND CANCER: STATE OF THE EVIDENCE AND FUTURE DIRECTIONS

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ABSTRACT

The ketogenic diet (KD) has been proposed as an adjunctive approach in cancer management, primarily through its impact on tumor energy metabolism. This review dissects the mechanistic basis of KD's potential effects, focusing on four interrelated domains: (1) glucose metabolism — restriction of carbohydrate intake lowers circulating glucose and insulin, potentially limiting glycolysis-dependent tumor growth; (2) mitochondrial function — ketone bodies may alter oxidative phosphorylation and reactive oxygen species dynamics, influencing cancer cell viability; (3) inflammation — KD's anti-inflammatory effects may modulate the tumor microenvironment; and (4) cell growth pathways — downregulation of mTOR and insulin-like growth factor signaling may impede proliferation. Evidence synthesis was conducted using databases including PubMed and Google Scholar, identifying both preclinical and clinical studies on glioblastoma, breast, and colon cancers. Preclinical animal models consistently show slowed tumor progression, yet human trials reveal variable and often modest benefits, with heterogeneity in study design, dietary adherence, and patient selection limiting interpretation. Furthermore, the possibility of tumor adaptation to ketone utilization remains an unresolved concern. Current evidence supports KD as biologically plausible but insufficiently validated for routine clinical use. Well-controlled, long-term trials are essential to clarify efficacy, optimal patient selection, and integration with standard oncologic therapies.

KEYWORDS:- Ketogenic diet, Cancer metabolism, Glucose restriction, Tumor growth inhibition, Ketone bodies, Dietary interventions, Cancer therapy.

INTRODUCTION

Carcinogenesis, the process by which normal cells become cancerous, is driven by a combination of genetic and epigenetic changes. These alterations trigger uncontrolled cell division and, in many cases, enable cancer to spread throughout the body. A key feature of this transformation is a shift in how cancer cells generate energy. Many tumors rely on the Warburg effect—a metabolic adaptation where cells favor glycolysis over oxidative phosphorylation, even when oxygen is available. This switch supports rapid tumor growth and helps cancer cells survive in low-oxygen environments.

By forcing the body into ketosis, where lipids are converted into ketones that act as an alternate energy source, the ketogenic diet (KD) is a high-fat, low-carb, moderate-protein diet. KD was first created to treat epilepsy, but it is currently being researched as a potential cancer supplemental treatment. This diet may interfere with the energy source that glucose-dependent cancer cells depend on by decreasing glucose availability and increasing ketone synthesis, which could decrease tumor growth.

There are several variations of the ketogenic diet, each with slight differences in macronutrient composition:

1. **Classic Ketogenic Diet (CKD):** Usually consisting of only 5–10% carbs, 15–20% protein, and 70–80% fat, this is the most stringent type of keto. It is frequently used in medicine, including to treat epilepsy.
2. **Targeted Ketogenic Diet (TKD):** Small amounts of carbohydrates can be consumed before or after exercise in this variant, which gives the body a brief energy boost while preserving ketosis throughout the remainder of the day.
3. **Cyclical Ketogenic Diet (CKD):** This method alternates between times when patients consume more carbohydrates and times when they are in strict ketosis. It is well-liked by athletes who want to

maintain the advantages of ketosis while replenishing their glycogen levels.

4. **High-Protein Ketogenic Diet (HPKD):** With fewer carbohydrates and a higher protein consumption (about 35–40%), this version differs from the others. It's a well-liked option for people who want to stay in ketosis and retain or gain muscle.

Mechanisms of the Ketogenic Diet in Cancer

A significant reduction in carbohydrate intake leads the body to go into a state known as ketosis, in which glucose is replaced as the main energy source by ketone bodies. By interfering with essential biological processes within cancer cells, this metabolic change may prevent tumor growth.[1] The following physiologically tenable theories have been put out to explain how the use of the ketogenic diet may affect the course of cancer:

1. **Limited Glucose Supply:** Cancers that lack metabolic flexibility and are unable to easily switch to alternative fuel sources for them this approach may be especially benefical. Cancer cells particularly those with high glycolytic activity, rely mostly on glucose for energy synthesis. By limiting carbohydrate intake, the ketogenic diet lowers systemic glucose levels, potentially depriving tumor cells pf an essential energy source.[1]
2. **Increased Ketone Production:** β-hydroxybutyrate is a key ketone body produced during ketosis that has drawn significant interest due to its role in regulating expression of genes. Research shows that it can inhibit histone deacetylase (HDAC) enzymes, which are involved in chromatin remodeling and activation of the oncogenes. Ketones may suppress genes that promote tumor growth through this mechanism by enhancing the expression of tumor suppression genes, which will create an environment that will help to limit the cancer spread.[2][3]
3. **Better Mitochondrial Function**: Cancer cells frequently have dysfunctional mitochondria, which affects how they metabolize substances. By promoting mitochondrial biogenesis and function, the ketogenic diet may make tumor cells more susceptible to oxidative stress and inhibit their ability to proliferate.[4]
4. **Reduced Inflammation** – It is commonly known that chronic inflammation contributes to cancer. It has been demonstrated that the ketogenic diet reduces systemic inflammation, which may help lower the risk and progression of cancer.[5,6]

Effects of the Ketogenic Diet on Various Cancer Types

1. Glioblastoma (Brain Cancer)

One of the most aggressive and glucose-dependent tumors is glioblastoma (GBM). Ketogenic diets (KDs) may help decrease tumor growth in glioma models, according to research. A systematic review indicated that diets decreasing blood glucose, such as KDs, effectively reduced tumor growth in animal experiments, with considerably larger advantages when combined with other therapy.[7] Another study shown that in mice models of GBM, combining a calorie-restricted KD with the glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) resulted in a notable mortality of tumor cells.[8] Even though clinical research on KDs for GBM is still in its infancy, interest in this strategy is continually rising. Twenty patients with recurrent GBM participated in the ERGO pilot study, which evaluated a KD and concluded that it was safe and controllable When used on its own, the ketogenic diet (KD) did not exhibit significant therapeutic benefit in clinical outcomes, as noted in an initial Phase 1 study.[7] However, another trial investigating KD in combination with standard treatment protocols reported a potential improvement in patient response and outcomes.[9]

The role of KD in managing glioblastoma multiforme (GBM) continues to be explored through ongoing clinical investigations. The safety and viability of combining KD with metformin and the experimental medication Paxalisib in patients with newly diagnosed or recurrent GBM is being assessed in a current Phase 2 trial. Furthermore, a different randomized controlled Phase 2 study seeks to determine whether following a ketogenic diet can enhance overall survival in patients with newly diagnosed GBM in comparison to results under conventional dietary guidelines.

2. Breast Cancer

Triple-negative breast cancer (TNBC) is a highly aggressive and metabolically active cancer and has shown the Warburg effect where tumor cells exhibit increase amount of glucose uptake.

This effect has spurred the interest in ketogenic diet(KD) where a low carbohydrate and high gfat nutritional approach is used as a means to disrupt the tumors energy supply. Research studies have shows that when KD is combined with other treatment it can significantly lower blood glucose levels. This drop in glucose has been linked to slow down tumor growth and long survival in animal models. The research suggest that suggest that cutting down carbohydrates in diet along with the bodys own glucose production might work together to stop the cancer from spreading.[10]

In addition, patients on the KD had higher levels of the anti-inflammatory cytokine IL-10 and lower levels of inflammatory markers like insulin and TNF-α. These results imply that KD may reduce inflammation associated with tumor growth and improve chemotherapy responsiveness.[11]

Some studies warn against it, while others point to possible advantages. Research indicates that KD does not always stop tumor growth. Not all preclinical research on the ketogenic diet (KD) and triple-negative breast cancer (TNBC) has been positive, despite some encouraging results. KD only momentarily slowed the growth of primary tumors and had no effect on metastatic progression in a number of TNBC models.

Moreover, emerging evidence suggests that elevated levels of ketone production might actually facilitate metastasis by promoting epithelial-mesenchymal transition (EMT), a key process in cancer dissemination.[12]

Ongoing clinical trials are investigating whether KD has therapeutic value in breast cancer management. One early-phase study is evaluating the effectiveness of combining KD with letrozole in patients with estrogen receptor-positive breast cancer. Another Phase I trial is exploring how KD, when paired with chemotherapy, may impact recurrence rates in individuals with stage IV breast cancer. These trials aim to clarify whether KD can be safely and effectively integrated into existing treatment regimens.

3. Colon Cancer

According to studies, colorectal tumor size and number were significantly reduced in mice given a KD. Increased levels of beta-hydroxybutyrate (BHB), a ketone body created during carbohydrate restriction that has been demonstrated to inhibit intestinal tumor growth, are primarily responsible for this impact. The anticancer effects, however, vanished after the diet was stopped, highlighting the necessity of ongoing dietary management to keep its advantages. The possibility of combining KD with traditional cancer treatments has also been investigated.

KD improved the efficacy of an investigational anticancer medication in pancreatic cancer animal models by restricting glucose availability, which effectively starves tumor cells and stops their growth. Despite the fact that this study concentrated on pancreatic cancer, the metabolic processes at play imply that treatment for colorectal cancer may benefit from comparable approaches.[13]

4. Lung Cancer

Lung cancer cells frequently undergo metabolic reprogramming to prioritize glycolysis and glutaminolysis over oxidative phosphorylation in order to meet their energy demands. Researchers are looking into dietary therapies like the ketogenic diet (KD) as possible supportive treatments as a result of this change in metabolic pathways. KD has demonstrated potential in improving the efficacy of traditional treatments in preclinical settings. In one study, for example, mice with human lung cancer xenografts showed better survival and slower tumor growth after receiving a KD in addition to radiochemotherapy. Increased oxidative stress in the tumor cells was partially blamed for these effects.[14]

The enhanced outcomes appeared to be linked to modulation of oxidative stress and systemic inflammation.[15]

While clinical evidence remains limited, ongoing trials aim to assess the therapeutic value of KD in lung cancer patients. The KETO-Lung trial, for example, is evaluating whether continuous adherence to a KD, combined with standard immunotherapy and chemotherapy, can improve clinical outcomes and quality of life in patients with squamous cell lung cancer. Another clinical study is investigating KD in conjunction with photodynamic therapy (PDT) to treat airway-obstructing lung tumors, based on the hypothesis that KD may increase tumor sensitivity to PDT.

Although human data are still emerging, preclinical results suggest that KD may inhibit lung cancer cell proliferation and potentiate standard treatments. Further well-designed clinical trials are necessary to determine its efficacy and safety in the clinical setting.

5. Pancreatic Cancer

Pancreatic cancer, known for its aggressiveness and poor prognosis, exhibits a high dependence on altered metabolic pathways. This characteristic has led researchers to explore the ketogenic diet (KD) as a potential adjunct to conventional therapies. Preclinical studies using pancreatic ductal adenocarcinoma (PDAC) models have yielded encouraging findings, particularly when KD is combined with chemotherapy. In one study, this combination significantly extended survival—tripling it compared to chemotherapy alone. While KD on its own had minimal impact on tumor growth, its integration with chemotherapeutic agents markedly enhanced treatment efficacy.

Further investigations have identified specific metabolic vulnerabilities in pancreatic cancer. For instance, in murine models, the combination of KD and eFT508 (tomivosertib)—a compound that inhibits the fat metabolism-related protein eIF4E—effectively suppressed tumor growth. This dual approach appeared to deprive cancer cells of their ability to utilize lipids for energy, leading to tumor regression.

Although clinical data remain limited, interest in the therapeutic use of KD in pancreatic cancer is growing. A Phase I trial involving patients with stage II–III disease assessed the safety and feasibility of KD during chemoradiation and reported favorable tolerability. Another early-phase study examining the effects of KD in combination with chemotherapy and radiation for locally advanced cases also found the diet to be manageable and potentially beneficial in targeting tumor metabolism.[16]

6. Prostate Cancer

Prostate cancer cells often undergo metabolic shifts that increase their reliance on fatty acid and glucose oxidation to meet energy demands. This metabolic plasticity has drawn attention to dietary interventions such as the ketogenic diet (KD) as a potential adjunctive treatment. Preclinical studies have shown that KD may

slow prostate cancer progression. In animal models, mice fed a carbohydrate-restricted ketogenic diet exhibited smaller tumor volumes and improved survival compared to those consuming a typical Western diet.

The main reason behind these effects is thought to be reduces availability of glucose which mainly limits the energy supply which tumor cells need to grow.[17] Researchers have also begun exploring how ketogenic diet may work along with immunotherapy. In one study a compound 1,3-butanediol which raises ketone levels along with cyclical inhibitors in prostate cancer models. This combination of both not only altered the tumor immune environment but also its epigenetic makeup buy helping the cancer cells to respond better to treatment.[18]

7. Liver Cancer

Liver cells often change the way they produce energy to help them grow and spread more quickly. Due to this, many researchers are exploring whether certain diets like KD could help slow the disease. Animal studies show that mice that were fed a ketogenic diet developed smaller tumors and lived longer than those on a regular diet. These effects mainly occur due to changes in how the cancer cells are processed and a drop in blood sugar levels, which makes it difficult for the cancer cells to grow.[19]

A meta-analysis and detailed review have supported these findings by showing how the KD- may reduce the development and progression of liver cancer in preclinical models. This suggests that dietary changes could play a role not just in treatment but also in prevention as well might be useful for prevention as well as treatment. However, there is still limited clinical data specifically in liver cancer patients. Early studies do suggest that KD is generally safe and well tolerated and may even improve quality of life while reducing some of the side effects associated with chemotherapy.

8. Ovarian Cancer

Because ovarian cancer cells often mainly rely on glucose for energy so researchers are exploring the KD as a possible treatment approach. By decreasing the glucose availability KD may cut off a key fuel source for these cells potentially showing their growth and improving the effects of standard treatments.

However results from early lab studies have been mixed. Some research suggests that an unrestricted KD might actually support the growth of certain ovarian cancers and doesn't always increase the effectiveness of drug like cisplatin. On other hand other studies have found that KD can improve how tumors respond to chemotherapy and also help to slow cancer progression. These mixed findings really show how complicated cancer metabolism can be, especially when trying to apply dietary changes in real world treatment. Still early results from clinical studies are encouraging.[20]

In one randomized control trail which involves women with ovarian and endometrial cancer, KD was found to be safe and didn't any negative affect on cholesterol levels compared to a lowfat diet. Many participants were able to stick with the diet adherence rates ranged from 57% to 80% which suggests that KD could be a practical and promising option for patients.[20]

9. Melanoma

Melanoma cells are known for their metabolic flexibility where they mainly rely on glycolysis but can also use fatty acids and ketone bodies for energy. Because of this adaptability many scientists are exploring whether ketogenic diets could as a supportive treatment. Recent animal studies have shown very promising results like KD not only have slowed the growth of tumor but also have boost the effect of standard cancer therapies. These effects may be due to diets ability to influence immune responses and alter how melanoma cells process energy.[22]

KD may not be the right fit for all types of melanoma. Some studies suggest that in certain genetic conditions, such as tumors with the BRAF V6000E mutation, a very high-fat ketogenic diet could actually make things worse by increasing the MEK1 activity and speeding the tumor growth. These findings show the importance of understanding a tumor's genetic profile before recommending dietary approaches like KD.

While early lab research suggests that KD might slow melanoma growth and improve standard treatments, its safety and effectiveness in humans is still unclear. More clinical studies are needed to find out whether KD can be used safely and effectively as a supportive therapy for melanoma patients.

10. Head and Neck Cancer

Head and neck cancers, especially HPV-negative types, are often marked by high glucose metabolism. Due to this, researchers are looking into the ketogenic diet (KD) as a possible supportive treatment. By lowering the glucose levels and encouraging the use of ketone bodies, KD may help to slow down tumor growth and improve the effect of conventional treatments. Preclinical studies have demonstrated that combining KD with chemoradiation therapy (CRT) improved survival and slowed tumor growth in mouse models of head and neck squamous cell carcinoma (HNSCC). These findings suggest that KD can be used as supportive therapy in conjunction with conventional therapy.[23]

In a Phase 1 trial, patients with advanced head and neck squamous cell carcinoma were enrolled to evaluate the safety and potential benefits of combining KD and CRT. While most patients were able to stick to the diet, a few patients experienced negative side effects like acute pancreatitis and hyperuricemia.[23] Another study was done where KD's effects were examined on body composition after radiation therapy and found that it

helped preserve muscle mass while also lowering the overall burden of treatment. These early results suggest that KD could play a role in easing some of the physical side effects linked to aggressive cancer treatment.[24]

DISCUSSION

The ketogenic diet (KD) is gaining interest as a potential approach to cancer treatment because of its ability to disrupt how tumors produce energy. By significantly reducing carbohydrate intake, it leads to shifting of body's main fuel source from glucose to ketone bodies through KD .This change may be particularly important for cancer cells that mostly depend on glucose to generate energy. While preclinical studies in different cancer models have shown mixed clinical outcomes To completely understand how KD affect tumor growth and how it might be used in treatment more research is needed in depth.

1. Metabolic Adaptation and Tumor Growth

Cancer cells often change the way they make energy to help them grow and survive longer. One common change is the Warburg effect, which occurs when tumor cells choose to produce energy using sugar, even when there is plenty of oxygen present. This adaptation helps them grow quickly and build what they need for cell growth. The ketogenic diet (KD), which is very low in carbohydrates, lowers the amount of sugar in blood. Since many cancers rely heavily on sugar for energy, this type of diet can slow down their growth. Early lab studies have shown that KD may be helpful in aggressive types of tumors like glioblastoma, breast tumors, and colon cancer.[1][4]

Besides cutting off the sugar supply that many tumors rely on like ketones especially one called β-hydroxybutyrate (BHB), may also help fight cancer more directly. Research has also shown that BHB can block enzymes called histone deacetylases (HDACs), which play a role in turning genes on and off and also include those involved in cancer growth. By blocking HDAC, ketones may help turn down cancer promoting genes and increase the activity of genes that slow tumor growth.[2][5] The finding highlight the need for more research into how switching the body's energy source from glucose to ketones might impact cancer development.

2. Mitochondrial Function and Oxidative Stress

To survive under stress, many cancer cells stop using their mitochondria properly; it is the part of the cell that is responsible for efficient energy production. Instead, they switch to the more or less efficient method of glycolysis to produce ATP even when there is enough oxygen; this switch is called the Warburg effect. The ketogenic diet (KD) may also help reverse this process. It is believed that KD can support the growth of new healthy mitochondria, a process called mitochondrial biogenesis. By doing this, it may restore normal energy production and make cancer cells vulnerable to oxidative stress.[4][6]

3. Inflammation and Immune Response

Chronic inflammation is essential for the development of cancer because inflammatory cytokines can promote tumor growth and metastasis. A diet high in ketones (KD) may have anti-cancer effects by reducing systemic inflammation, according to numerous studies. KD may be able to disrupt inflammatory signaling pathways that support tumor growth by lowering levels of inflammatory cytokines such as TNF-α and IL-6.[5]

4. Combination with Conventional Therapies

One of the most intriguing features of the ketogenic diet (KD) is its potential to improve the effectiveness of conventional cancer treatments like chemotherapy, radiation, and immunotherapy. Cancer cells often develop resistance by altering their metabolism, which enables them to persist and multiply despite treatment. KD may help overcome this resistance and make the tumors more amenable to treatment by limiting the availability of glucose and altering the metabolism of cancer cells to use ketones.[26]

For example, preclinical studies on glioblastoma have demonstrated that KD can boost the effectiveness of the chemotherapy drug temozolomide. According to research on breast cancer, KD may make tumor cells more sensitive to radiation by altering energy metabolism and generating more reactive oxygen species (ROS), which would increase the oxidative stress caused by radiation therapy.[27]

Therefore it's important to consider carefully before mixing KD with cancer treatments. Although it may enhance the efficacy of treatment, there is a chance that it will have unforeseen consequences for healthy cells, especially those engaged in tissue repair and immune system activity. Future studies should focus on improving dietary guidelines and treatment regimens to maximize positive impacts and reduce adverse effects.

5. Clinical Evidence and Human Trials

A small number of human trials have explored its effects across different cancers, with mixed results. Some studies report improvements in quality of life, reduced tumor size, and better tolerance to conventional treatments, while others show no significant clinical benefits.[28][29]

A major challenge in translating animal model findings to human patients is the variability in cancer biology. Tumor heterogeneity, differences in metabolic dependencies, and patient-specific factors such as genetics and comorbidities can all influence how individuals respond to KD[30].Moreover, there is no standardized ketogenic diet protocol for cancer patients. Variations in macronutrient composition, treatment duration, and patient adherence may impact outcomes.[31] Strict carbohydrate restriction, essential for maintaining ketosis, can be difficult for some patients, and potential side effects—such as gastrointestinal discomfort,

electrolyte imbalances, or nutrient deficiencies—must be carefully managed.[32] Long-term safety data is also lacking, underscoring the need for further research to assess KD's sustainability and effectiveness in cancer management.[33]

6. Challenges and Future Directions

Despite its potential as a cancer treatment, the ketogenic diet (KD) has a number of issues that need to be resolved.

1. Personalization & Patient Compliance :Many patients find it challenging to maintain stringent carbohydrate restriction to maintain ketosis, which raises questions about the diet's long-term viability. Furthermore, the way that various tumors respond to KD may differ according on their metabolic features. To optimize its therapeutic advantages, a customized strategy based on each patient's unique metabolic profile and tumor biology may be required.[34]

2. Insufficient Clinical Data and the Requirement for Sturdy Trials:Despite promising preclinical evidence, a thorough knowledge of KD's effectiveness in treating cancer has been impeded by the absence of extensive, carefully planned clinical trials. To ascertain its actual therapeutic effect, future research should give priority to randomized controlled trials (RCTs) with robust clinical outcomes, such as overall survival and progression-free survival.[35] Furthermore, examining KD in conjunction with radiation, immunotherapy, and targeted therapies may uncover synergistic benefits and increase the range of possible uses.[35]

3. Mechanistic Understanding Gap: Although studies have found metabolic changes linked to ketosis, the molecular processes behind KD's anti-cancer benefits are still not fully understood. To further understand how fatty acids, glucose, and ketones interact in the tumor microenvironment and affect important signaling pathways, more research is required.[37] Optimizing KD as a cancer treatment approach will require a deeper comprehension of these pathways.

CONCLUSION

Numerous cancer types have showed potential with the ketogenic diet, especially those with high glucose reliance. Clinical evidence in humans is still scarce and contradictory, despite preclinical research in animal models indicating substantial therapeutic promise. KD may increase the efficacy of traditional therapies including immunotherapy, radiation, and chemotherapy, but more study is required to create precise guidelines for its use in cancer treatment, especially well-designed clinical trials. To ascertain the safety and feasibility of a high-fat, low-carb diet as a standard therapeutic method, future research must also thoroughly assess the potential long-term hazards and the variability in patient responses.

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