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Commentary

Scientific and Technical Limitations Hinder the Clinical Potential of the Ketogenic Diet for Cancer Treatment

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COMMENTARY

Over 9 million people worldwide are expected to die from cancer each year [1], and despite efforts to improve treatment paradigms, cancer treatment remains especially challenging. Because cancer prognosis can vary significantly based on tumor location and disease stage, treatment paradigms that are effective in a variety of cancers are needed. Cancer is often treated with a combination of surgical resection, radiation therapy and chemotherapy, but each of these treatment methods has clinical limitations. Surgical resection is effective for removing large solid tumors, but it is less effective at removing diffuse tumors or treating metastatic disease. While radiation therapy is effective at treating a variety of cancers, lifetime radiation exposure limits may hinder its long-term efficacy. In contrast to localized treatments such as surgical resection and radiation therapy, chemotherapy is a systemic treatment that can target both primary tumors and metastatic disease. Unfortunately, anticancer drugs are often toxic to patients, and these drugs may lack enough selectivity to effectively kill tumors while sparing the surrounding normal tissue. Although significant research efforts are ongoing to improve existing cancer treatment methods, alternative treatment methods are needed to improve cancer treatment paradigms and reduce mortality.

Dietary treatments are an emerging approach in which a clinician modulates a patient's nutritional intake rather than their pharmacological treatment. Since these approaches initiate a systemic effect in patients without causing toxicity, dietary treatments provide oncologists with a unique alternative to traditional cancer treatment methods. In one study, calorie restrictive diets were shown to reduce carcinogenesis in rodent models of cancer [2]. However, in clinical studies of malnourished cancer patients, increased caloric intake was correlated with shorter hospital stays, decreased readmission rates and improved quality of life [3,4]. Based on these observations, it is evident that a patient's diet can play a significant but paradoxical role in cancer treatment. Thus, dietary treatments that restrict the growth of cancer cells without significantly affecting normal cells hold promise to reduce carcinogenesis, decrease tumor growth, enhance the efficacy of conventional cancer treatments and improve patient outcomes.

One type of dietary treatment that has shown promise in oncology is the ketogenic diet (KD), a well-known diet in which carbohydrate intake is significantly restricted (<50 g/day). By carefully following the KD, patients are expected to achieve a low blood glucose state called ketosis in which energy production is shifted from glucose to ketone bodies. The KD was previously developed to treat childhood epilepsy patients [5], but it has received popular attention as a weight loss strategy. The KD is generally well-tolerated in patients and can be applied concurrently with a wide variety of cancer therapies [6]. Due to its wide-spread popularity, several versions of the KD with varying macronutrient profiles and recommended daily caloric intakes have been developed for weight loss. For cancer treatment, researchers typically select previously developed KD protocols that are already in clinical use.

The KD is believed to selectively target cancer cell metabolism by limiting energy sources for glucose-sensitive cancer cells without affecting hypoglycemia-tolerant normal cells. In patients following the KD, sufficient glucose cannot be provided to cells to maintain their required metabolic activities, and cells must overcome this energy deficit by metabolizing ketone bodies as a primary energy source. Normal cells can easily metabolize ketone bodies, but cancer cells struggle to adapt to this metabolic change, and consequently carcinogenesis and tumor growth are hindered in ketogenic conditions [7,8].

One significant benefit of the KD over other dietary treatments such as calorie restriction is that its anticancer properties are not dependent on daily caloric intake. Many cancer patients undergo significant wasting over the course of their treatment, and a calorie-restrictive diet may exacerbate this condition. In contrast, obese patients with certain types of cancer may want to lose weight to reduce their future cancer risk [9]. By following a KD, cancer patients could adjust their daily caloric intake to prevent wasting while still inhibiting carcinogenesis. In one literature analysis, carcinogenesis inhibition was observed in eight out of nine animal studies investigating the KD, while mixed effects on carcinogenesis were observed in animal studies on calorie restrictive diets [10].

Adherence to the KD on its own and in combination with other

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cancer treatments have improved cancer outcomes in both *in vivo* studies and early clinical trials. Zou et al. demonstrated that the anticancer effects of rapamycin in both primary breast cancer and lung metastasis mouse models were enhanced by the KD [11]. In advanced cancer, one study noted that the effects of the KD on patient survival were modest, but the diet improved patients' quality of life [12]. A phase I clinical trial demonstrated the potential of the KD to enhance radiation treatment for locally advanced lung and pancreatic cancers, but poor patient compliance to the diet was noted to limit treatment efficacy [13]. Notably, the KD has been an especially promising treatment for glioblastoma (GBM), an aggressive brain cancer that has limited treatment options and poor overall survival. Abdelwahab et al. demonstrated that GBM-bearing mice following the KD had increased survival compared to mice following a standard diet, and the effects of radiation treatment were enhanced in mice following a KD compared to a standard diet [14].

Despite its previous successes in various studies, significant scientific and technical obstacles must be overcome for the KD to become a clinical cancer treatment option. Schwartz et al. noted several specific issues that prevent the wide-spread adoption of the KD in GBM treatment, including the lack of standardized KD protocols for GBM and the need to monitor ketosis by frequent blood glucose level measurements [15]. Because patients who are prescribed the KD in clinical studies are not typically given explicit meal plans, they may not achieve ketosis on their own. While frequent blood glucose level measurements can be used to monitor ketosis in patients, the blood drawing required for these measurements may be undesirable for cancer patients with poor health. The development of explicit KD protocols for cancer treatment could improve patient compliance and reduce the need for blood glucose level monitoring. Moreover, an improved understanding of the relationship between blood glucose levels and tumor growth is needed. Because the KD was developed to treat epilepsy rather than cancer, its specific carbohydrate intake restrictions may be stricter than what is required to inhibit tumor growth. Thus, more detailed, optimized KD protocols for specific cancer types, stages and treatment statuses could be developed to remove any unnecessary dietary restrictions while maintaining treatment efficacy. In addition, a greater understanding of the effects of temporary dietary non-compliance, or so-called cheat days, on carcinogenesis and tumor growth in patients is needed.

While the KD has shown promise in mouse models of cancer and early clinical trials, its clinical applications are limited by poor patient compliance, sub-optimal KD protocols for cancer patients and demanding testing to monitor the ketosis state of patients. As a dietary treatment for various types of cancer, the KD was effective both as a sole treatment method and in combination with chemotherapy and radiation therapy. Because it is not typically harmful to patients on its own, the KD poses limited drawbacks in comparison to traditional cancer treatments. In the future, three main areas should be addressed for the KD to become an effective cancer treatment. Initially, more research is needed to develop a nuanced understanding of the effects of blood glucose levels on carcinogenesis and tumor growth. Based on this research, more optimal KD protocols based on specific types and stages of cancer may be developed to improve KD efficacy while reducing the challenges of patient compliance. To support these optimized dietary regimens, additional translational methods are needed to verify patient compliance, and improved support systems are needed for patients to use in developing KD protocols. By accomplishing these three goals, the potential clinical benefits of the KD to reduce cancer mortality may be achieved.

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