

A Nutritional Perspective of Ketogenic Diet in Cancer: A Narrative Review

Camila L. P. Oliveira, MSc; Stephanie Mattingly, PhD; Ralf Schirrmacher, MD; Michael B. Sawyer, MD; Eugene J. Fine, MD; Carla M. Prado, PhD, RD*

ARTICLE INFORMATION

Article history:

Submitted 29 June 2016
Accepted 2 February 2017

Keywords:

Ketogenic diet
Cancer
Metabolism
Treatment
Nutrition

2212-2672/Copyright © 2017 by the Academy of Nutrition and Dietetics.

<http://dx.doi.org/10.1016/j.jand.2017.02.003>

*Certified in Canada.

ABSTRACT

The predominant use of glucose anaerobically by cancer cells (Warburg effect) may be the most important characteristic the majority of these cells have in common and, therefore, a potential metabolic pathway to be targeted during cancer treatment. Because this effect relates to fuel oxidation, dietary manipulation has been hypothesized as an important strategy during cancer treatment. As such, the concept of a ketogenic diet (KD) in cancer emerged as a metabolic therapy (ie, targeting cancer cell metabolism) rather than a dietary approach. The therapeutic mechanisms of action of this high-fat, moderate-to-low protein, and very-low-carbohydrate diet may potentially influence cancer treatment and prognosis. Considering the lack of a dietetics-focused narrative review on this topic, we compiled the evidence related to the use of this diet in humans with diverse cancer types and stages, also focusing on the nutrition and health perspective. The use of KD in cancer shows potentially promising, but inconsistent, results. The limited number of studies and differences in study design and characteristics contribute to overall poor quality evidence, limiting the ability to draw evidence-based conclusions. However, the potential positive influences a KD may have on cancer treatment justify the need for well-designed clinical trials to better elucidate the mechanisms by which this dietary approach affects nutritional status, cancer prognosis, and overall health. The role of registered dietitian nutritionists is demonstrated to be crucial in planning and implementing KD protocols in oncology research settings, while also ensuring patients' adherence and optimal nutritional status.

J Acad Nutr Diet. 2017; ■:■-■.

DURING THE 1920S, OTTO WARBURG OBSERVED that most cancer cells, regardless of oxygen availability and functional mitochondria, capture and metabolize large amounts of glucose and convert it to lactate rather than fully oxidizing it (as in the case of healthy respiring cells) to carbon dioxide. This phenomenon, now termed the Warburg effect,¹ represents an inefficient use of glucose because the theoretical yield of adenosine triphosphate (ATP) generated by aerobic glycolysis (2 ATP/mol glucose) is lower than that theoretically obtained through mitochondrial respiration (36 ATP/mol glucose). This inefficient use of glucose may be countered by an increased rate of glucose uptake, which alters levels of the intermediates and substrates associated with glycolysis, and consequently promotes growth, survival, proliferation, and maintenance of tumor cells.^{2,3} This distinctive metabolic feature of cancer cells is the basis for the imaging of tumor tissue by positron emission tomography using the radio-labeled glucose analogue ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG).⁴

Considering that cancer is a highly heterogeneous disease because of its distinct genotypes, the Warburg effect is an important characteristic that the majority of cancer cells have in common, representing a susceptible metabolic pathway

that could be targeted during cancer treatment. Despite being known for several decades for its broad applicability to diverse cancers, there have been few systematic clinical investigations of the phenomenon,⁵ and the development of treatment strategies based on an understanding of the implications of the Warburg effect have likewise been limited.

The Warburg effect relates to fuel oxidation, so dietary manipulations have been hypothesized as important strategies to prevent and treat cancer. As such, the ketogenic diet (KD) has emerged as a potential metabolic therapy (as opposed to simply a dietary approach) with the aim of exploiting the aforementioned metabolic vulnerability of cancer cells; that is, overreliance on glycolysis.⁶ Although the evidence of its influence on cancer is limited, a KD approach has been extensively studied for the treatment of epileptic seizures.⁷ The initial application of KD to epilepsy stemmed from the observation that seizures were reduced or absent when affected individuals were fasting.⁸ A KD dietary pattern can simulate a fasted state because reliance on fat metabolism is a key characteristic under both dietary conditions.^{9,10} Although the mechanisms of action are not fully understood, metabolic consequences of a KD as they relate to cancer include its influence on cancer cell epigenetics and on

RESEARCH

growth-factor signaling pathways, including insulin, reactive oxygen species production, and angiogenic factors, and the inflammatory state,^{6,11} as described by Klement and Kammerer.⁶ Its use has been extensively studied in cell and animal models,¹² and a few clinical trials in human beings have aimed to establish feasibility and safety and to assess efficacy.^{13,14}

In general, the KD is characterized by high-fat, moderate-to-low protein, and very-low carbohydrate content. The conventional fat to carbohydrate and protein ratio of this diet is 4:1 and 3:1, respectively, which gives a macronutrient distribution of approximately 90% fat, 2% carbohydrate, and 8% protein.¹¹ However, alternative macronutrient distributions have been recently developed to increase flexibility and palatability (eg, lower fat to carbohydrate and protein ratio, medium-chain triglyceride KD, and low glycemic index treatment).^{11,15} The increased fat metabolism and limited carbohydrate metabolism of a KD induce a state of physiologic ketosis with increased production of ketone bodies in the blood (18 to 90 mg/dL [1 to 5 mmol/L]),¹³ decreased glucose (65 to 80 mg/dL [3.6 to 4.4 mmol/L])^{11,16} and insulin (6.6 to 9.4 μ U/L [45.8 to 65.2 pmol/L]),^{11,16} and maintenance of blood pH levels (pH=7.4).^{11,16}

The macronutrient distribution range of KD is not ideal for maintenance and promotion of health and prevention of chronic diseases according to the Acceptable Macronutrient Distribution Range recently published in the Dietary Guidelines for Americans (10% to 35% of protein, 45% to 65% of carbohydrate, and 20% to 35% fat).¹⁷ However, its therapeutic mechanisms of action may transcend this concern in clinical settings. In fact, beneficial effects of KD have been observed in the context of conditions such as epilepsy¹⁸ and other neurologic diseases,¹⁹ obesity,²⁰⁻²⁷ diabetes,²⁸⁻³¹ polycystic ovary syndrome,³² cancer,¹¹ respiratory conditions,³³ and cardiovascular disease.^{26,34-38} In these and other contexts, decreased morbidity and mortality may exceed potential acute or chronic side effects observed with a KD dietary pattern.¹¹ In view of the potential influence of a KD on cancer treatment or prognosis and the lack of a dietetics-focused narrative review on this topic, this review describes the evidence related to the use of this diet in cancer therapy research, either as a standalone treatment or in conjunction with other therapies, focusing on the nutrition and health perspective.

METHODS

The focus of this review is to describe original human studies conducted in individuals diagnosed with cancer who are consuming a KD. A literature search was performed in PubMed/MEDLINE from its inception until May 2016. The search strategy consisted of two separate components, each involving key words related to "cancer" and "ketogenic diet" individually. The key words in each component were linked using "OR" as a Boolean function, and the results of the two sections were combined by utilizing the "AND" Boolean in final search. Nonoriginal articles, in vitro studies, studies with animal models, studies with children, studies in which cancer originated because of a previously diagnosed disease, and studies in languages other than English were excluded. All studies meeting the inclusion criteria were reviewed—from case studies to randomized controlled trials—despite

statistical approach. Titles and abstracts of retrieved studies were screened to select potentially relevant articles. Full text of the remaining studies was then analyzed independently to determine whether they met the established criteria. References of eligible articles were then searched manually for additional articles that could have been missed by the electronic search. A flow chart of the literature selection process is shown in the [Figure](#).

Studies Investigating KD in Cancer

A total of 14 studies published between 1988 and 2016 that included 206 individuals (94 women, 106 men, and 6 not defined) assessed effects of the KD in cancer patients (see the [Table](#)). The age and sex of participants were not mentioned in one study.³⁹ The mean sample size was 15 participants (range=1 to 78 participants). Study designs included 2 clinical trials,^{40,41} 1 controlled clinical trial,⁴² 1 randomized controlled trial,⁴³ 5 case reports,⁴⁴⁻⁴⁸ 1 retrospective study,³⁹ 1 prospective single-arm pilot study,¹⁴ 1 pilot clinical study,¹³ 1 systematic prospective cohort study,⁴⁹ and 1 prospective observational pilot study.⁵⁰

Cancer types varied substantially among studies. The use of concurrent standard cancer treatments were not mentioned in four studies.^{40,41,44,49} Concurrent treatment included chemotherapy (one study)⁴³ and radiation+chemotherapy (four studies).^{14,39,46,47} Five studies used KD as the sole therapy.^{13,42,45,48,50} The duration of the dietary interventions ranged from 5 days to 12 months, and consisted of oral KD,^{13,39,43,47,48} oral KD plus supplements (vitamins, minerals, carnitine, arginine, highly fermented yogurt drinks, vitamin D-3, and/or n-3 fatty acid),^{14,40,44-46,50} and parenteral KD feeding.^{42,44} No details of diet administration were provided in two studies.^{41,49}

Nine studies assessed the effects of KD on tumor metabolism and/or disease progression.^{13,14,41,42,44,46,48-50} Among them, 2 reported negative results,^{46,48} 2 showed diverse results among participants,^{13,49} 4 did not report any difference between treatments,^{14,42,44,50} and 1 demonstrated an alteration in cancer cell metabolism (not related to ¹⁸F-FDG) associated with the KD intervention.⁴¹ The remaining five studies assessed effects of the KD on metabolic and health outcomes as well as its safety and feasibility.^{39,40,43,45,47}

KD and Disease Progression

The two studies reporting negative results were case studies conducted in patients with glioblastoma (World Health Organization grade IV).^{46,48} In the first study, an older woman followed a KD for 14 days,⁴⁶ compared with a 12-week intervention in two adult men.⁴⁸ Despite discrepancies in the length of the dietary intervention, cohort, and diet characteristics, both studies failed to demonstrate efficacy, which could be explained by the aggressiveness of the tumor type being studied (1.5-year median survival).^{51,52} In addition, Schwartz and colleagues⁴⁸ reported a positive expression of ketolytic enzymes in participants' tumor cells, suggesting an ability to metabolize ketone bodies to produce energy. These findings are supported by a recent study in human beings reporting that malignant glioma cells are genetically heterogeneous, and have different ketolytic and glycolytic enzyme expression.⁵³ Therefore, as concluded by the authors, expression of ketolytic enzymes may also

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات