The Ketogenic Diet for Cancer Patients: A Narrative Review

by

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A paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Department of Nutrition

Chapel Hill, North Carolina

December 6, 2018

Approved by:

[redacted] December 5, 2018

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MPH Paper Advisor

Abstract

Use of the ketogenic diet in cancer patients is currently being explored in all stages and types of cancer. The ketogenic diet could influence human metabolism in such a way as to reduce tumor growth, increase efficacy of standard cancer treatments, and reduce side effects of those treatments. The goal of this review was to examine the available evidence on the effects of the ketogenic diet in human cancer patients. Including the only randomized controlled trial to date, 15 articles were reviewed and summarized to help determine the state of the science. As research in this area is emerging, most of these studies used small sample sizes and were conducted in patients with advanced cancer stages. However, they differed in design, diet intervention, and measurement of outcomes, including method and frequency of biomarkers and diet adherence. Although most results from these studies are mixed, all studies support the safety and feasibility of the ketogenic diet for cancer patients. Those studies that examined body composition reported positive effects from the ketogenic diet, such as preservation of muscle mass and increased physical functioning. In addition, certain biomarkers point to a positive effect of the diet on cancer proliferation; however, it is unknown if the effects of the diet differ between specific cancer cell types and if these effects influence tumor growth. More research is needed to elucidate the mechanisms behind the effects of the diet, and to determine the differences in metabolism across specific cancer cell types before this diet can be recommended.

Introduction

Despite improvements in early detection and treatment, cancer is still the second leading cause of death worldwide (1,2), and approximately one in six individuals will be diagnosed with cancer in their lifetimes (2). The ketogenic diet is currently being explored for use in people with all types and stages of cancer with or without standard treatments such as radiation, chemotherapy, or immunotherapy. Though the ketogenic diet was developed as a treatment for epilepsy in children (3,4), it has potential be helpful for cancer due to the biochemical effects of the diet on human metabolism (5–11).

The ketogenic diet intends to mimic the state of fasting by severely restricting carbohydrate intake in order to induce ketosis (4). During times of fasting, and thus while following the ketogenic diet, ketones are produced from fatty acid degradation providing healthy cells with an alternative energy source, thereby reducing the need for glucose. The classic ketogenic diet is composed of a 4:1 ratio of grams of fat to carbohydrate plus protein (90% of kJ or calories from fat, 6% from protein, and 4% from carbohydrate). Since this distribution of macronutrients does not meet the protein requirements for most adults (12), a more liberal diet is often used, such as a 3:1 gram ratio (82% of kJ or calories from fat, 12% from protein, and 6% from carbohydrate) or the modified Atkins diet (3). The modified Atkins diet is a 0.8:1 ratio of grams of fat to carbohydrate plus protein (65% of kJ or calories from fat, 30% from protein, and 5% from carbohydrate, with less than 20 grams carbohydrate per day for adults) and has been found to be more feasible and sustainable in adults while still allowing ketosis (3,13–15).

Given the potential of the ketogenic diet to improve outcomes in cancer patients, research is emerging in both animals and humans. Animal studies have shown promise for the ketogenic diet to attenuate tumor growth, reduce muscle wasting, and sensitize various tumor types to traditional treatments (16–21). However, some animal studies have shown tumor progression in a

specific cancer type while on the ketogenic diet (the BRAF V600 positive melanoma model) (22). In another animal study, metastasis was observed when exogenous ketones were administered to mice with breast cancer xenografts (23).

In humans, the ketogenic diet could reduce blood glucose levels, limiting fuel availability to cancer cells since these cells may not be able to efficiently use ketones for energy (5–11). The diet may also inhibit growth signals due to the low amount of carbohydrate consumed on the diet (5–11). Therefore, the ketogenic diet could affect cancer in three ways: 1) the diet could reduce tumor growth, 2) it could increase the efficacy of standard cancer treatments by inhibiting production of endogenous antioxidants generated from increased glycolysis, and 3) it could reduce or prevent treatment-limiting and potentially life-threatening side effects, such as muscle wasting or cachexia (5–11) (i.e., multi-factorial sarcopenia with weight loss typically more than 5% of usual body weight) (24). Pre-clinical trials support these benefits, but the effectiveness of the ketogenic diet must be further evaluated in human cancer patients before it can be provided as a viable treatment option.

Despite these potential benefits, few studies have focused on the ketogenic diet in human cancer patients; therefore, this review presents the available relevant studies on this topic. While systematic and narrative reviews of the ketogenic diet in cancer patients have been conducted, they have been broad in scope, including individual case reports (9,25–29), interventions other than a ketogenic diet (25,28,30), or only one cancer type (28). Two studies also included pediatric patients (27,29) who may exhibit different metabolism and responses to dietary interventions than adults (31). To date, previous reviews have not included randomized controlled trials of the ketogenic diet in cancer. Thus, the following review aims to examine the current state of the science on the effects of the ketogenic diet in cancer patients and to help identify important objectives for future research.

Methods

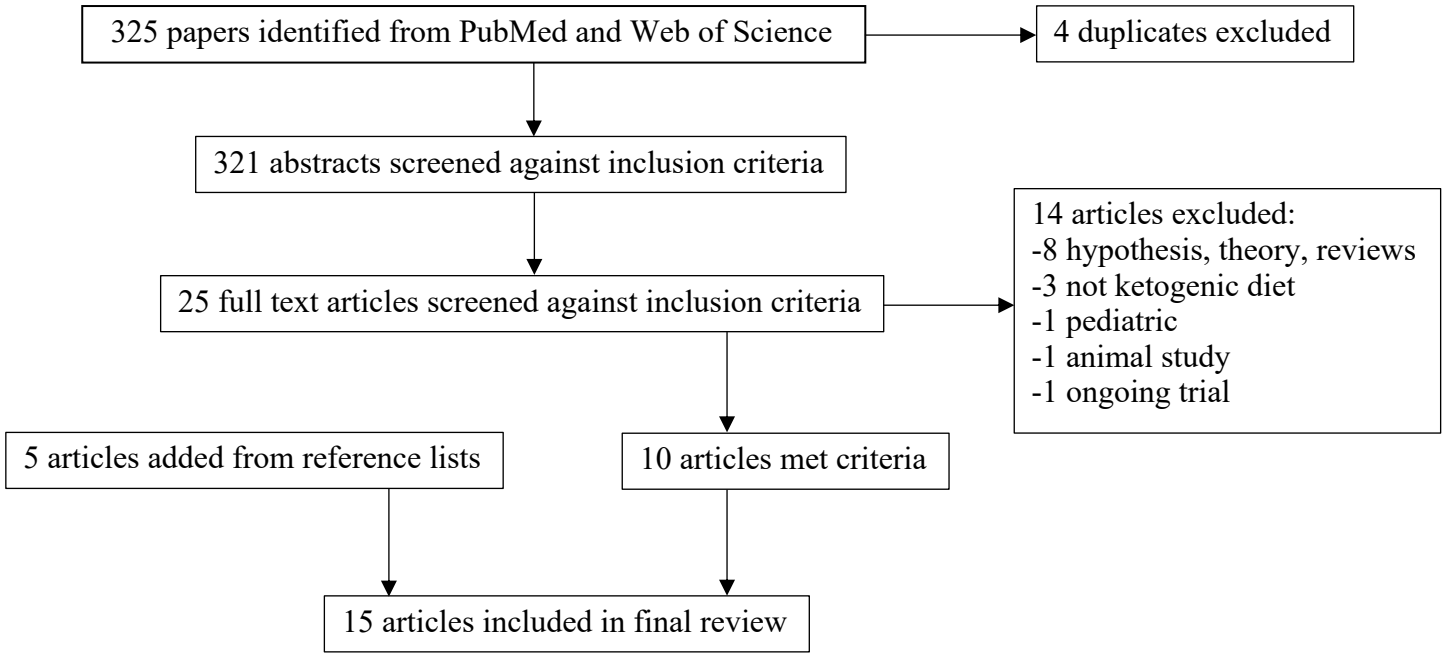
A literature search was conducted on September 22, 2018 and included all papers published until this date. Two databases were used, PubMed and Web of Science, to search for studies involving the ketogenic diet in human cancer patients. Search terms were formulated with help of a librarian and included variations of ketogenic, ketones, or modified Atkins and cancer, tumors, or neoplasms using Boolean terminology. The exact search terms for each database can be found in Appendix A. Criteria for inclusion were studies relating the use of a ketogenic diet or modified Atkins diet with adult human cancer patients while in treatment, after treatment, or as sole treatment. Papers in a language other than English were excluded, as were *in vitro* studies or studies using solely animals. In order to describe the current state of the evidence, this review includes all studies from the search that evaluated the use of the ketogenic diet in cancer patients, with the exception of individual case reports. Since case reports are important to help inform future studies but are not sufficient to determine generalizable outcomes for specific treatments (32), these were not included.

Titles and abstracts of all papers resulting from the search were reviewed. Those papers that did not meet inclusion criteria were removed. The remaining articles were read in full; again, excluding those that did not meet the inclusion criteria. Additional qualifying articles were identified from reference lists of included papers and others used for background research. Data abstracted from these studies include: study design, country, cancer type, concurrent cancer treatments, age, sex, race, number of participants, length and details of the dietary interventions, if and how ketosis was measured, adverse events, and primary and secondary outcomes.

Results

The search in PubMed resulted in 176 articles, which was further reduced to 149 articles after excluding articles that were not in the English language or human studies. The Web of Science search resulted in 176 articles. Of these combined 325 articles, four were duplicates and removed. Of the remaining 321, ten articles met the inclusion criteria. Five additional articles were included from papers used for background research. In total, 15 articles were included in this review.

Figure 1: Flowchart of literature selection



Study characteristics

Study characteristics and outcomes are detailed in Table 1 and major points are discussed in the following sections. The 15 articles that comprise this review were published between 1988 and 2018. Study designs include one randomized controlled trial (33,34); one non-randomized, three-arm controlled trial (35); one observational case series (36); one observational pilot (37);

and one retrospective review (38). Two studies utilized cross-over trials (39,40) and three were single-arm pilot studies (9,34,35). Four studies were single-arm clinical trials (14,15,43,44), two of which used retrospective data (43) or study drop-outs for comparison (44). Studies were conducted mostly in Germany (n=5) and the U.S.A. (n=5). Race was only reported in three studies. Two included all (14) or majority (33) Caucasian participants, while one included an equal number of Caucasian and African American participants (41).

Across 14 studies, 156 participants attempted the ketogenic diet. Study participant age ranged from 30-78 years. Participants in nine studies had advanced cancer (14,15,17,36–38,40,41,43), while in four studies, cancer stage ranged from early to advanced (33,35,42,44). One study did not report cancer stage, but all patients were considered cachectic, with 32% mean weight loss and anorexia pre-study (mean energy and protein intake was 55% and 28%, respectively, of estimated needs) (39). Six studies included various cancer sites (14,36,37,39,41,42). Of the studies that focused on single cancers, most included glioblastomas or other brain cancers (15,17,38,43), while the rest included gastrointestinal (35), head and neck (40), lung and pancreatic (44), and endometrial and ovarian cancers (33). Radiation, chemotherapy, or immunotherapy were concurrent treatments in seven studies (15,17,33,38,42–44), while four used the ketogenic diet as sole therapy (14,35,37,41). Three studies did not report concurrent treatment status (14,37,41). Of the studies that used the ketogenic diet as sole treatment, three were administered in metastatic or previously treated patients who had no further treatment options (14,37,41). The other was administered in patients of varying cancer stages who were treatment naïve, shortly before surgery (35).

Measurement of Ketosis

Ketosis was measured in eleven studies (14,15,17,33,37–39,41–44), however, each used different criteria. Ketone levels used to determine ketosis ranged from "detectable" to ≥ 4 mmol/l, and studies varied in the frequency of measurement and the vehicle used for analysis (i.e., blood, urine, or both). Urine ketones alone were measured in three studies (15,17,37), while three studies only measured blood ketones (14,39,41). Four studies measured both blood and urine ketones (33,38,42,44). One study measured both urine and brain ketones (43). Frequency of measurement varied from twice per day to every four weeks. One study used ketosis as a measure of dietary adherence and determined that one of five participants did not adhere to the diet, while two adhered intermittently, and two adhered strictly (43). Two studies reported dietary adherence in participants that did not achieve ketosis (17,42). Another assessed dietary adherence by both dietary recall and ketone levels, and reported that 80% of the participants had achieved dietary adherence (33).

Intervention

The intervention evaluated in all studies was a carbohydrate restrictive diet, although the specifics differed in each. The diet composition ranged from 4% of total kJ or calories per day from carbohydrates to as much as 16% (39). Intervention times ranged from five days to 12 months; the most frequent length was 12 weeks. Most commonly, participants were responsible for purchasing groceries and preparing meals that adhered to the diet. Education and support in the form of dietary counseling and meal plans from a registered dietitian or physician were provided in ten of the 14 studies (14,15,17,33,36–38,41–43). Three interventions were patient-directed using available resources on the ketogenic diet (36,38,42). One study (44) prepared and provided all the meals, while two studies had controlled delivery via nasogastric tube (39) or parenteral nutrition (35). One study did not discuss details of the intervention (43). No study

reported providing behavioral counseling or skills training to assist participants in changing their diet, although one indicated that frequent counseling by a registered dietitian, ketogenic formulas and meals, and cooking classes would be of benefit for future patients (42).

Primary Outcomes

Safety and feasibility

Because the study of the ketogenic diet for cancer patients is in its infancy, the majority of studies measured safety and feasibility as primary outcomes (n=9) (14,15,17,37–39,41,42,44). One measured feasibility as the ability of the participants to achieve ketosis (defined in this study as serum levels > 0.2 mmol/l) and was successful in all five participants (39). Seven studies measured feasibility by the number of participants who withdrew (15 out of 89) because of diet intolerance, side effects, or inability to follow the prescribed diet (14,15,17,37,41,42,44).

Six studies measured feasibility by monitoring adverse events; the most common were mild constipation (15,37,41,44), mild to moderate fatigue, nausea, and bloating (14,37,38,41). Two studies withdrew three participants due to hyperuricemia, dehydration (44), and “excessive” weight loss and weakness (37). One study reported no significant difference in quality of life scores before the diet and after the diet (14), while another reported a slight improvement in insomnia and emotional functioning, while other parameters declined slightly (37).

One study examined the possibility of future clinical trials of the ketogenic diet in people with brain cancer (15). Four of six participants who had completed a 12-week trial of the diet reported they would participate in another clinical trial, while only one would do so if the trial was randomized. A separate poll of 172 persons with brain cancer who had not participated in the study found that 66% would be willing to participate in a future clinical trial, but only 36% would do so if the trial was randomized (15). Another study that polled its participants found that

while three of six thought the diet was difficult, all felt "good" or "very good" on the diet, and continued a variation of a low-carbohydrate diet after the study ended (42).

Metabolic effects

Metabolic effects of the ketogenic diet were reported as primary outcomes in eight studies (35,36,38–41,43,44). In one crossover trial, blood glucose was reduced by a mean of 14% after 7 days of the ketogenic diet (39), and by a mean of 58% in a retrospective review with diet adherence ranging from three to twelve months (38). However, 14 days of parenteral administration of the ketogenic diet resulted in no significant difference in blood glucose (35).

Similarly, serum lactate and pyruvate, byproducts of glucose metabolism, decreased by 46% and 40%, respectively, after administration of the ketogenic diet in Fearon et al.'s crossover trial (39). Lactate levels in tumor tissue also declined from baseline by a range of 0.16 to 3.73 mmol/l in tumor tissue in head and neck cancer patients after five days of the diet (40).

Jansen and Walach (36) measured reduced levels of transketolase-like-1 (TKTL-1) (-150 mean change in EDIM-TKTL-1 scores), an oncogene marker that is associated with enhanced glucose metabolism, proliferation, and poor prognosis (45). Zahra et al. (44) discovered significant increases in mean carbonyl levels by 0.4 nmol/mg compared to baseline levels in participants on the ketogenic diet, a measure of increased oxidative stress.

Insulin level was a primary outcome for two studies (39,41). Fine et al. (41) found that ketone levels ranging 10 to 35 times higher than baseline were associated with 70% to 90% reduction in serum insulin levels. However, insulin levels and insulin-like growth factors (IGF-1 and IGF-2) were found to have no significant association in a study of 10 patients (41). Fearon et al. (39) found no significant difference in insulin levels between a normal diet and the ketogenic diet, even though blood glucose was reduced.

Artzi et al.'s study (43) attempted to determine if brain tissue utilizes ketones and if urine was an accurate way to measure ketosis. While all five participants had achieved at least intermittent ketosis as assessed by urine level, ketones were only detected in brain tumor tissue once out of 27 total scans and in tumor-free tissue in three scans in two patients.

Anthropometrics

Three studies reported anthropometrics as primary outcomes (33,35,42), two of which noticed significant loss of fat mass with preservation of muscle mass (33,42). Using dual-energy X-ray absorptiometry (DXA), Cohen at al.'s randomized controlled trial showed that ketogenic dieters lost significantly more fat mass than controls (5.2 kg versus 2.9 kg), with no significant difference in loss of lean muscle mass (33). A prospective trial (42) showed significant increases in relative fat free mass of 0.29% to 0.49% per week in three of four measurable participants using bio-electrical impedance analysis (BIA). However, Rossi-Fanelli et al. (35) found no difference in muscle or fat mass from baseline in either the lipid or carbohydrate arms after a 14-day intervention.

Tumor progression

Only one study measured tumor progression as a primary outcome. Rossi-Fanelli et al. (35) measured tumor proliferation using thymidine sampling and found a non-significant trend in an increase (32.2%) of replicating cells in participants receiving 100% dextrose parenterally, and a non-significant decrease (-24.3%) in participants receiving 80% lipid solution.

Secondary Outcomes

Tumor progression and survival

Though no study was powered to determine the efficacy of the diet on disease status, nine studies included some measure of tumor progression or survival as a secondary outcome, attributing observed effects to various reasons (14,17,36–38,41–44).

One observational study demonstrated an association between decreased tumor progression and adherence to the diet as determined by dietary recall (ketones were not monitored) (36). Another found that those with stable disease had the longest diet adherence, and some participants who had achieved ketosis had progression of disease (37). A prospective study found that participants who adhered to the diet, but had low levels of ketones, showed partial tumor regression (42). However, ketosis was associated with greater overall survival in three studies (17,38,41), one which found three-fold higher ketone levels in participants with partial remission of glioblastoma than in those with progressive disease (41). One study found positive tumor responses among dieters with the greatest weight loss (10% or more), but no difference in levels of ketosis or blood glucose in those that had stable disease or partial remission and those that had progressive disease (14). In contrast, two prospective studies showed no effect of the diet on tumor progression or on progression-free survival (43,44).

Metabolic effects

Eight studies reported biochemical markers as secondary outcomes (14,15,17,33,37,40,42,44). In a randomized controlled trial, Cohen et al. (33) found higher levels of ketosis inversely associated with serum insulin levels and IGF-1, but did not find significant differences in IGF-1 or its binding protein (IGFBP-1) between those following a ketogenic diet and controls.

Four studies (14,18,32,42) found no significant difference in blood glucose levels from baseline after the diet. Zahra et al. (44) found mixed results, but one study reported improvements in blood glucose levels (37), and another reported decreased amplitude of blood

glucose from the diet (40). One study showed a negative correlation with serum ketone and glucose levels (42). No other studies reported significant differences in any biomarkers.

Anthropometrics

In seven studies reporting weight changes as a secondary outcome (14,15,17,37,39,41,44), all but one (39) reported weight loss (ranging from 2% to 10%). The only study that resulted in weight gain included cachectic patients who were fed isocaloric regular and ketogenic diets for seven days each, but showed an average weight gain of 2 kg only after administration of the ketogenic diet (39). Only one of these seven studies showed no significant difference in weight, fat mass, or arm circumference between pre- and post-diet (15).

Physical Functioning

Physical functioning was reported as a secondary outcome in three studies. Two studies reported improvements in physical functioning post-ketogenic diet (34,39), while a third found no difference between baseline and study completion (44).

Discussion

Studies conducted thus far support further research into the efficacy of the ketogenic diet for cancer patients. With the support of biochemical theory, *in vitro*, and animal studies, trials in cancer patients have begun to test the safety, feasibility, and effects of this diet. While difficult for some to follow, the majority of patients in the studies included in this review (141 out of 156) were able to adhere to the diet for the study period. The majority of withdrawals occurred at four to eight weeks, though patients in three studies followed the diet for one year or longer (36,38,43). While adherence to the diet likely depends on several factors such as treatment side effects and individual preferences, adherence for at least four weeks suggests that use of the ketogenic diet concurrently with standard cancer treatments is feasible for patients. Generally

unchanged or improved biomarkers demonstrate that the diet is safe and has potential to be beneficial for cancer patients.

With the exception of one study (44), this review found that the ketogenic diet has the potential to reduce or even reverse the muscle wasting that often accompanies cancer and standard cancer treatments (17,33,39,42). One of the main nutrition concerns for a cancer patient undergoing treatment is rapid weight loss because this usually indicates loss of muscle mass, undermining the patient's treatment, quality of life, and even survival (7). Most of the studies monitored weight changes, but only four (17,33,39,42) measured muscle mass or protein turnover. Cohen et al. (33), reporting on the only randomized controlled trial to measure the effects of the ketogenic diet on body composition to date, demonstrated loss of fat mass with preservation of muscle mass in patients following the ketogenic diet as compared to the control group. Future studies would benefit by including measurements of fat-free mass or physical functioning to better understand the ketogenic diet's effect on body composition. There is evidence that in a cachectic patient, the number of calories consumed may not have a direct effect on weight (39,46), pointing to the potential metabolic alterations taking place in some cancer patients. Addressing these changes through diet composition may be of benefit, as seen in Fearon et al.'s study of cachectic patients (39).

Along with the reduction of muscle wasting, studies showed that the ketogenic diet is associated with reduced blood glucose and metabolites of aerobic glycolysis and gluconeogenesis, namely pyruvate, lactate, and TKTL-1 (36,39). These markers are indicative of reduced cancer cell activity and show promise for a positive effect of the ketogenic diet on tumor growth. However, these were small sample sizes with short intervention duration, and few studies measured these outcomes. Additionally, the progression-free survival and overall survival of the patients included in these studies do not show a clear influence of the ketogenic diet on

tumor progression. Studies that reported positive effects on tumor growth attributed these to various reasons: the intervention diet (36,37,42), the level of ketosis (17,38,41), the amount of weight loss while on the diet (14), or an immunotherapy drug (43). Future studies would benefit from establishing a standard of monitoring ketosis, byproducts of glucose metabolism, and diet adherence in order to better understand the mechanism behind the effects of the diet.

The ability of the ketogenic diet to improve the efficacy of cancer treatments by increasing oxidative stress while reducing endogenous antioxidants remains to be seen in humans. While one study tested this theory and found elevated carbonyl levels as a marker of increased oxidative stress in three dieters undergoing radiation and chemotherapy or immunotherapy (44), more evidence is required to support this theory in cancer patients.

Although not the goal of these interventions, the majority of participants who followed the ketogenic diet experienced weight loss. Only five of eleven studies with participants responsible for their own meals reported gathering dietary recalls (15,33,41–43), while only two reported the caloric intake of participants (41,42). Collecting food diaries or dietary recalls would be beneficial in future studies to help differentiate effects from spontaneous calorie reduction, as occurred in Fine et al. (41), or from diet composition, as seen with Fearon et al. (39).

The strengths of this review lie in the systematic approach used and the clinical lens through which study outcomes were viewed. Any benefit of the ketogenic diet for the cancer patient must be considered. While the results of this review point to the appropriateness and benefit of further study of the ketogenic diet for cancer patients, the finding should be considered in the context of some limitations. Although the literature search was conducted with only two databases, a systematic approach was used with consultation from a librarian with expertise in systematic reviews. While five qualifying articles were not included in the initial search results,

additional papers were identified for inclusion by searching reference lists of articles resulting from the search.

An in-depth critique of cancer cell types and results from animal studies was beyond the scope of this review but warrants further examination. Studies of specific cancer types in animal models have demonstrated tumor growth and metastasis with administration of the ketogenic diet or exogenous ketones (22,23). In addition, it is unclear if specific cancer cell types may be able to use ketones for energy, as ketones have been detected in brain tumors of both animals and humans (43,47). Future larger trials that are adequately powered to evaluate the efficacy of the ketogenic diet are warranted. However, these studies would benefit from a more detailed evaluation of the metabolism of different cancer cell types to further elucidate the potential harms and benefits from the implementation of the ketogenic diet in cancer patients.

In conclusion, the results from this review support further study into the effects of the ketogenic diet in cancer patients. There are at least 16 clinical trials underway studying the ketogenic diet and various cancer types, including brain, breast, prostate, endometrial, lymphoma, and one on body composition (48). The diet holds promise as an adjuvant treatment to reduce muscle loss, improve tolerability of concurrent therapies, and improve quality of life. However, clarity about the effects of the diet on specific cancer types, as well as results of safety and efficacy from larger studies, are necessary before the ketogenic diet can confidently be recommended as a viable option for cancer patients.

Acknowledgements

Gratitude to Dr. Carmina Valle for her guidance and expertise during the research and writing process. Dr. Valle assisted in determining inclusion and exclusion criteria and editing, and provided guidance regarding study design, approaches to reviewing the literature, the

presentation of the findings, and the format of the final paper. Arida Emrys provided editing assistance.

Conflict of Interest

The author has no conflicts of interest to disclose.

Funding

No funding was received in support of this review.

Table 1: Study characteristics

Author/ date/ country	Study design	# analyzed	Cancer type/stage	Mean age	Sex	Race	Length of intervention	Intervention/ implementation	Concurrent treatment	How study measured ketosis	# who attained ketosis	Adverse events	Primary endpoint measured	Primary outcome(s)	Secondary outcome(s)
Rieger et al. (17), 2014 Germany	Single arm prospective pilot	13 measured urine ketones 20 enrolled 17 evaluated	Recurrent glioblastoma Advanced disease	57 median 30-72 range	65% F	Not reported	12-16 weeks (up to 124 weeks f/u)	KD: ≤60g CHO/day No calorie restrictions Yogurt/oil drinks provided (500ml/day). Diet education, recipes, food facts, and rules were provided Participants prepared meals at home, no eating plans provided	Bevacizumab (n=7) Steroids (n=11)	Urine Ketones detectable in ≥50% measurements Tested: 2-3 x week	8 achieved "stable" ketosis (ketones detected ≥50% of the time) 5 achieved ketosis <50% of the time	Hunger, sugar craving in first week Diet intolerance: 3	Feasibility-% discontinued diet due to intolerability	15% (3/20) discontinued diet due to "negative effects on quality of life"	Mean 2.2% weight loss NSD in BG, chol. LDL, HDL, TG Median PFS: 6 wks for stable ketosis (n=8) 3 wks w/o stable ketosis 20 wks for bevacizumab + diet Overall median survival: 32 weeks from enrollment (n=17)
Artzi et al. (43), 2014 Israel	Single arm prospective cohort with retrospective data used for comparison	9 (5 dieters, 4 GB retrospective controls)	4 with GB (advanced stage), 1 with gliomatosis cerebri (low grade)	51	56% F	Not reported	2 months to >31 months 3 yrs on diet for gliomatosis cerebri	KD: 4:1 ratio based on KetoCal powdered formula. Specific diet plan was tailored to each participant	Bevacizumab + steroids for GB KD only for gliomatosis cerebri Comparison group: TMZ, BVZ, or rindopepimut	Urine Ketones >2 (units not indicated) Tested: daily H-MRS: every 2 months	Urine: 4 achieved high ketoses (>4) H-MRS: detected in 2 participants	Intermittent diet compliance: 2 Diet intolerance: 1	Metabolic brain changes using H-MRS	Ketones detected in brain 4 times in 2 patients (3 in one – 2 in NAWM, once in lesion), 1 in other- in NAWM) No association of urine ketone level and brain ketones	SD in one patient with low grade gliomatosis cerebri PR or SD in 3 GB patients after 2 months (attributed to immune therapy)
Cohen, Fontaine, Arend, Alvarez et al. (33), 2018 Cohen, Fontaine, Arend, Soleymani et al. (34), 2018 U.S.A.	RCT w/ parallel arm	45 (20 ACS; 25 KD)	Endometrial, ovarian, various stages	ACS: 58.6 KD: 61.5	100% F	Cauc/ AA/ Asian ACS: 17/3/0 KD: 22/2/1	12 weeks	KD: 70:25:5 fat: protein: carbohydrate Control: ACS diet (high fiber, low fat) Participants responsible for meal preparation RD provided Individual diet education, weekly counseling, recipes and meal plans	25% (11) were receiving chemo, type not reported	Urine Ketones >0.5 mmol/L Tested: First 2 weeks: daily remaining 10 weeks: weekly Serum BHB at baseline and 12 weeks	20 KD participants (80%)	KD: Constipation, mild fatigue Unable to adhere to diet ASC: 2 KD: 1	Body composition (measured with DXA)	KD: Greater total (5.2 kg vs 2.9 kg) and visceral fat loss (177 g vs 126 g) NSD in lean muscle mass loss	KD vs ACS: Lower serum insulin (6.7 uU/mL vs 12.1 uU/mL, p<0.01), c-peptide (2.0 ng/mL vs 3.0 ng/mL, p<0.001) NSD in blood glucose Higher BHB (0.91 mmol/L vs 0.25, p<0.001) NSD for IGF-1, IGFBP-1

															Increased physical functioning (Medical Outcomes Study Short Form-12 Health Survey) reduced starch and fat cravings (Food Cravings Inventory) increased salt cravings (Visual Analog Scale for Appetite) NSD in mental functioning or appetite
Fearon et al. (39), 1988 U.K.	Non-randomized crossover trial Subjects as own controls	5	lung (2), ovarian (1), gastric (2) All considered cachectic, staging not reported	61	60% F	Not reported	14 days	KD (days 7-14): 70% MCT, 14% protein Regular diet (days 0-6): 55% CHO, 31% fat Tube feeds provided	Not reported	>0.2mmol /L serum acetoaceta te + BHB Tested: every other day during KD	5 within 24 hours of KD	None reported	Ketosis, BG, nitrogen-balance, concentration of GNG substrates	KD: ketones in all >0.2mmol/L BG: 14% decrease Pyruvate: 40% decrease Lactate: 46% decrease. NSD in LFT, FFA, glutamine, N-balance, BUN, creatinine, whole body protein turnover NSD in insulin levels (14.3 vs 15.3 uU/mL, p>0.1)	2 kg mean weight gain after KD Increase 1 grade in performance scale (WHO) after KD
Zahra et al. (44), 2017 U.S.A.	Phase 1 prospective clinical trial Used dropouts for comparison	9 enrolled, 6 withdrew 3 evaluable	NSCLC (n=2): stage III-IV; pancreatic: (n=1), stage Ia-III	67.5	100% F	Not reported	Lung: 42 days (n=2) Pancreas: 34 days (n=1) 5-6 weeks intended	KD (4:1) 90:8:2 ratio for fat: protein: carbohydrate Meals provided for participants	lung: carboplatin + paclitaxel + radiation pancreas: gemcitabine + radiation	≥0.6mg/dl Urine ketones and serum ketones Tested: daily finger stick blood,	3	See primary outcomes	Tolerability (Common Terminology Criteria for Adverse Events version 4.0), carbonyl levels	Lung: 4 dropped out due to difficulty adhering to diet, constipation, fatigue, bloating, nausea	NSD in weight change in dieters and drop-outs Mean weight loss for lung: 6% Mean weight loss for pancreas: 10%

										weekly venous serum				1 with dose-limiting grade 4 hyperuricemia Pancreas: 1 with dose-limiting grade 3 dehydration Carbonyl levels: increased from 1.0-1.4 nmol/mg	BG: increased in NSCLC (~30 mg/dl), decreased slightly in pancreas (~1 mg/dl) Karnofsky performance status not improved with KD NSD in PFS between dieters and drop-outs. Median survival of drop-outs: 22 months Median survival of KD dieters: 17.7 months
Fine et al. (41), 2012 U.S.A.	Prospective pilot	10 (9 had pre-existing progressive disease)	Varied: breast (2), lung (2), colorectal (3), fallopian tube (1), esophagus (1), ovary (1); Advanced, incurable	63	70% F	4 AA 4 Cauc. 1 Asian 1 Hispanic	26-28 days	Goal: 5% carbohydrate Actual: ~9% carbohydrate Participants required to purchase and prepare meals. Provided with instructions and menus	None	Serum BHB tests compared to baseline as a measure of insulin inhibition Tested: weekly	All 10 achieved a mean ketone level above baseline	See primary outcomes	Adverse events, insulin levels Common Terminology Criteria for Adverse Events, version 3.0 used	Grade 2 fatigue (n=5), grade 1 constipation (n=5) grade 1 leg cramps (n=1 reversible) Ketosis inversely associated with serum insulin levels (regression coefficient = -1.67, p=0.026) NS association of insulin levels and IGF-1 and IGF-2 (regression coefficient -0.10, p=0.38 and -0.17, p=0.21, respectively)	2.5%-6.1% weight loss in 9/10 participants (mean 4%) All had ~35% unintentional calorie reduction No difference in caloric intake or weight loss in PD and SD or PR PD: n=4 SD: n=5 PR: n=1 SD and PR had 3-fold higher ketone levels than did PD

														NSD in BG, electrolytes, renal function	
Martin-McGill et al. (15), 2018 U.K.	Single arm prospective trial for service evaluation	6 (4 completed study)	High-grade glioma with prior surgical resection, stages III-IV	47.5	100% M	Not reported	12 weeks	Modified KD: 70% fat, 20 g CHO/day (3-5% of calories), no protein restriction Participants provided with 7-day meal plan, diet literature, recipes, urine ketone sticks, and ketone diaries. Had contact with RD at weeks 1,3,6,9,12	TMZ, lomustine, dexamethasone	Urine Ketones ≥4 mmol/L Tested: Month 1: 2 x day Month 2: 1 x day Month 3: 2 x week	4 (1 had 3-week break due to hospitalization)	See primary outcomes	Tolerability and feasibility in NHS Patient willingness to participate in RCT	2 withdrew: 1 for dietary preferences, 1 for deterioration of condition Constipation (n=2) resolved with linseed/ flaxseed Increase in grocery bill Willingness to participate in future clinical trial/RCT: From questionnaire (n=172): 66% (n=114)/36% (n=62) From study's participants post trial: 66% (n=4)/16% (n=1)	NSD in weight, BMI, fat mass, and arm circumference pre- and post-diet. NS increases in chol, LDL, HDL, TG BG measured, not reported
Schmidt et al. (37), 2011 Germany	Prospective observational pilot	13/16 3 withdrew, 5 adhered to diet entire study	Varied, advanced/metastatic Ovarian (n=4) Breast (n=1) HNC (n=1) osteosarcoma (n=1) esophagus (n=1) pancreas (n=2) thyroid (n=2) colon (n=1) endometrial (n=1) lung (n=1) stomach (n=1)	50.4	75% F	Not reported	12 weeks	KD: ≤70g CHO/day (20g/meal) + 2 liquid snacks: 250 ml highly fermented yogurt (8mL vegetable oil mixture 10 g milk protein) Diet education, diet manual, exchange list, and recipes provided. Participants responsible for shopping and meal preparation	None	Urine Ketones ≥0.5 mmol/L in ≥50% of measurements Tested: 1 x day in morning	6 (3 dropped out due to progression of disease before end of study)	See primary outcomes Unable to adhere to diet: 3 1 dropped out due to excessive weight loss 2 deaths 6 PD	Feasibility QoL assessed by EORTC QLQ-C30 version 2	Insomnia, emotional functioning improved, all other QoL parameters declined at least slightly Constipation, diarrhea, low appetite, N/V, fatigue	Mean 2 kg weight loss Improvements in chol, CRP, BG, LFT Increase in TG, Cr (WNL). BG: mean 103 mg/dl (baseline) to mean 93 mg/dl (end of study) Reduced albumin (WNL) PD: 3 (w/ ketosis) withdrew SD: 5 (adhered to diet entire

															study, 3 w/ ketosis)
Tan-Shalaby et al. (14), 2016 U.S.A.	Single arm prospective trial	11/17 (4 completed study)	Varied, advanced Bile duct (n=1) Glioblastoma (n=1) Astrocytoma (n=1) Prostate (n=1) Melanoma (n=3) Renal (n=1) Colon (n=1) HNC (n=2) Liver (n=1) Pancreas (n=1) Lung (n=2)	65	100% M	Cauc.	16 weeks	MAD: 20-40 g CHO/ day no kcal or protein restrictions Advice on grocery shopping and menu planning provided	None	Serum Ketones detected Tested: every 4 weeks	All 11 Ranges: 0.28-4.13 mmol/L	Weight loss-mean 7.3 kg (7.7%) (n=8 of 11) Hyper-uricemia (n=7 of 11) Hyperlipidemia, pedal edema, anemia, pruritis, hypoglycemia, hyper- and hypokalemia, hypomagnesemia, fatigue, flu like symptoms (n=2 of 11) Unable to adhere to diet: 1	Safety and feasibility assessed by EORTC QLQ-C30 version 3	NSD in QoL scores between baseline and end of study	10% weight loss, decrease in BMI NSD in any serum values from baseline (day 2) (BG, chol, HDL, LDL, TG, BUN/Cr, Cr, albumin, uric acid) 3 patients continued diet beyond study and "significantly" extended survival times 80, 116, and 131 weeks from enrollment
Jansen and Walach (36), 2016 Germany	Systematic, prospective observational case series	11 on KD 78 total (77 had TKTL1 measured)	Breast (n=18) Prostate (n=16) colon (n=9) melanoma (n=2) lung (n=5) HNC (n=5) other (n=23) Stages curative (72%) palliative (19%) end stage (9%)	68.3	55% M	Not reported	13 months	Fully KD (n=7) Partial KD (N=6) No KD (n=65) As determined by dietary recall Participants instructed on the potential benefits of KD and informed about a company that provides ketogenic food products	Not reported	Not measured	Not measured	Not reported	TKTL1 and Apo10 and tumor status/ progression KD and tumor status and progression	Trend in reduction of TKTL1 and improvement in tumor status from baseline in those adhering to KD Probability of 4% improvement in tumor status with each 0.034 unit decrease in TKTL-1 values No effect of KD on Apo10, no correlation with tumor status Not powered for significance	DP: No end-stage achieved "Full KD," 1 achieved "Partial KD" 4 palliative pts adopted "Full KD": 1 had full remission (metastatic breast), 1 had SD (recurrent breast), 1 had PD (astrocytoma, received steroids), 1 lost to follow-up Those who started KD had initial PR, but DP once stopped KD Significant correlation between adopting "Full KD" and

															improvement in disease
Rossi-Fanelli et al. (35), 1991 Italy	Three arm control trial	27 (9 in each arm)	GI, stages I-IV (esophageal n=9), gastric (n=9), colorectal (n=9)	39-78 (range)	52% M	Not reported	14 days	Arm A: TPN, 100% dextrose, amino acids 0.24 g/kg body weight Arm B: TPN, 80% lipid, 20% dextrose, amino acids 0.24 g/kg body weight Arm C (control): isocaloric, isonitrogenous oral diet Diet implemented parenterally	No treatment prior or during	Not measured	Not measured	No adverse events reported	Influence of parentally supplied energy substrates on tumor cell proliferation and host nutritional status	NSD in cancer cell proliferation between arms, despite trend for 32.2% increase in glucose arm, and 24.3% decrease in lipid arm NSD in blood glucose or triglycerides levels before and after diet in any arm Reduction in lymphocytes in both glucose and lipid arms NSD in anthropometric measurements	None reported
Klement and Sweeny (42), 2016 Germany	Prospective pilot	6	Breast, rectum, prostate, lung, stages I-IV	60	67% M	Not reported	Mean 48 days (range 32-73 days)	0.8:1 to 1.8:1 determined from dietary recall Self-administered “KD” with dietary counseling 1 x week and education support 1 received ketogenic drinks	Radiation/ chemo + radiation	Urine ketones detectable (home) Serum (3 x during study) >0.3 mmol/L	4	No adverse events attributed to diet	Feasibility Body composition via BIA	All lost weight (significant in 2) n=4 of 6 had reliable BIA indicating loss of FM (0.28 to 0.68 kg/week) and stable FFM n=3 of 4 had significant increase in % FFM (0.29 to 0.49 % per week) 3 with decreased (-0.13 to -0.15 l/week) 1 with increased intracellular water (0.18 l/week) No other markers of hydration or body water	NSD in serum values: CBC, HDL and LDL, BG, insulin, IGF-1, TSH. Significant negative correlation between serum BHB and glucose (Spearman’s coefficient = -0.035, p=0.05) Increase in appetite loss (n=3), fatigue (n=2), nausea (n=2), diarrhea (n=2) attributed to RT/RCT PR: n=5 Slight PD: n=1 (metastatic lung, rapid

														changes (TBW, ECW) Diet analysis and lack of ketone measurement in 2 participants indicate difficulty with diet adherence 3 said diet was difficult All felt good or very good on diet All followed a KD or variation after treatment	progression once off diet and completed treatment)
Schroeder et al. (40), 2013 Germany	Prospective cohort with participants as own control	10/11 evaluable (1 male with equipment failure was not included in data)	HNSCC, stage III and IV	11/12	90% M	Not reported	5 days	Not defined Implementation of diet not reported	Not reported	Not measured/ reported	Not measured/ reported	Not measured/ reported	Lactate and pyruvate concentration in tumor and tumor-free mucosa	3/10 pts: tumor lactate levels decreased on KD by 0.16 mmol/l to 3.73 mmol/l) pyruvate stable or increased L/P ratio was constant in tumor-free mucosa, declined in tumor tissue in 7/9	On KD: all pts showed decline in amplitude of blood glucose
Champ et al. (38), 2014 U.S.A.	Retrospective review	Total: 53 KD: 6 Unspecified or standard diet: 47	Glioblastoma multiforme, grade III-IV	54	M/F (ratio not reported)	Not reported	3-12 months of KD. F/U up to 20 months	KD: carbs < 50g /day to <30 g/day and limiting protein if not achieving ketosis. Pt-driven diet but "several" tracked diet using online software Physician support provided if needed	Radiation and TMZ (temozolomide) RT, cetiranib and TMZ (n=1) Decadron (n=3)	Urine, serum Tested: Daily urine for 2 weeks, daily finger stick, biweekly serum Ketosis confirmed by treating	6 Unable to adhere to diet: N/A	Grade I constipation (n=2) Grade I fatigue (4 during RT) Grade II fatigue with kcal restriction (30%) n=1 Kidney stones (1 incident) 1 DVT (MTHFR def)	Safety, BG	BG 122 for standard diet, 84 for KD (before treatment KD avg was 142.5) Wt loss: 1, 5, 13, 27, 46 lbs (last 2 intentional, 1 on kcal restriction)	Disease progression: At median f/u of 14 months: 4 of 6 patients alive, 3 patients recurred, 1 patient no sign of recurrence at 12 months (on kcal restricted KD for 7 months, lost most weight, no steroids)

	physician via logs	Toxicities assessed using Common Terminology Criteria for Adverse Events, version 4	For all pts on KD mean time to recurrence/ progression was 10.3 months

GB: glioblastoma, KD: ketogenic diet, specifics follow, BHB: beta-hydroxybutyrate, NSD: non-significant difference, NAWM: normal appearing white matter, H-MRS: proton magnetic-resonance-spectroscopy , PD: progressive disease, SD: stable disease, PR: partial remission, GNG: gluconeogenesis, MAD: modified Atkins diet, TPN: total parenteral nutrition

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Appendix A: Search terms utilized per database

The search term used for PubMed: “(ketogenic OR ketone OR ketones OR ketosis OR "modified atkins") AND (diet OR diets OR dietary OR dieting OR nutrition) AND (cancer OR cancers OR oncolog* OR tumor OR tumors OR tumours OR tumour OR neoplas*) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR "clinical trial"[tw] OR "controlled trial"[tw] OR "random allocation"[tw] OR randomized[tw] OR randomly[tw] OR blind[tw] OR blinded[tw]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])” to help capture clinical trials involving humans. The search resulted in 176 articles, which was further reduced to 149 articles using English language filters and human studies.

The search term used for Web of Science: (ketogenic OR ketone OR ketones OR ketosis OR "modified atkins") AND (cancer* OR oncolog* OR tumor* OR tumour* OR neoplas*) resulted in 10,185. This was refined by using the term ("clinical trial" OR "control* trial" OR RCT), resulting in 147 articles.