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REVIEW ARTICLE

Systematic review: isocaloric ketogenic dietary regimes for cancer patients

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Abstract The efficacy and benefits of ketogenic diets (KD) have recently been gaining worldwide and remain a controversial topic in oncology. This systematic review therefore presents and evaluates the clinical evidence on isocaloric KD dietary regimes and reveals that evidence supporting the effects of isocaloric ketogenic dietary regimes on tumor development and progression as well as reduction in side effects of cancer therapy is missing. Furthermore, an array of potential side effects should be carefully considered before applying KD to cancer patients. In regard to counseling cancer patients considering a KD, more robust and consistent clinical evidence is necessary before the KD can be recommended for any single cancer diagnosis or as an adjunct therapy.

Keywords Cancer · Ketogenic diet · Nutrition · Cancer diet · Low carbohydrate · Oncology

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Introduction

Cancer diets are a controversial topic in oncology. Many patients try to adapt their diets in order to fight cancer, reduce side effects and improve their prognosis [1]. While many physicians will not recommend extreme diets such as the total cure by Breuss (42 days drinking only vegetable juice), the ketogenic diet (KD) seems to remain attractive from the professional point of view [2–4].

The KD is an established, non-pharmacologic treatment utilized in the treatment of intractable childhood epilepsy [5]. Its use was first documented in 1911 by French Physicians Guelpa und Marie. In 1921, Cobb and Lennox from Harvard University observed a reduction in seizure in patients after 2–3 days of fasting. This effect was thought to stem from metabolic changes induced by a state of starving or shortage of carbohydrates. In this state, ketone bodies become the main fuel for the brain's energy and force the body to burn acid-forming fat. In the same year, Wilder proposed that ketonemia could be achieved either by starvation or with a diet designed to mimic the body's biochemical response to starvation. He suggested that the diet could be maintained for a much longer period of time than starvation and coined the term "ketogenic diet." In 1925, Peterman documented a KD plan similar to that used today: 1 g of protein per kilogram of body weight with 10–15 g of carbohydrates (CHO) daily. The remaining calories required to meet individual energy needs were derived from fat. Peterman also documented the importance of individualized close management of the diet. In 1938, due to the discovery of diphenylhydantoin, the popularity of the KD declined rapidly as researchers shifted focus onto the new antiepileptic drugs. Consequently, fewer dietitians were trained to apply the KD. However, interest in the KD resurged in 1990 when a team from John

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Hopkins University successfully treated a child with intractable epilepsy [6, 7]. Retrospective and prospective studies and well as a few review articles began to explore the effectiveness of the KD for the treatment of intractable childhood epilepsy [8–11]. In 2005 and 2008, the first well-designed controlled and randomized controlled trials were published [12, 13]. Concurrently, researchers began to explore the mechanisms, efficacy, safety, and therapeutic actions of the KD for other diseases such as cancer, diabetes mellitus, cardiovascular diseases and neurological diseases like Alzheimer's and multiple sclerosis.

The KD became interesting for cancer patients as scientists gained more and more insight into pathways within tumor cells. Thus, the Warburg hypothesis was re-introduced into scientific discussions. While Warburg postulated that an increase in glycolysis induces carcinogenesis, scientists today hypothesize that genetic mutations cause cancer and that cancer cells preferentially metabolize sugar. Preclinical data suggest that the insulin pathway, including insulin, insulin-like growth factor 1 (IGF-1) and the IGF receptor IGF-1R, can be associated with cancer initiation and progression. This pathway is upregulated through dietary consumption of carbohydrates, and the minimization of these dietary sources in general or with a KD is one potential mechanism [14]. Ketogenic diets for cancer patients are therefore implemented with the aim to reduce the energy production of cancer cells, thus decreasing tumor proliferation [15, 16].

The aim of our review was to systematically assess the clinical evidence on isocaloric ketogenic dietary regimes (isocaloric dietary regimes are aimed to maintain weight which is essential for cancer patients undergoing therapy [17]) and derive evidence-based recommendations for counseling cancer patients with respect to this regimen.

Methods

The systematic literature search was performed in October 2016 and included different approaches: A comparative search of Medline and EMBASE was done using OVID, and the databases CINHAL, ERIC, PSYCHINFO and SOCINDEX were mined using EBSCO. For cancer, a controlled vocabulary ("Neoplasms") was combined with free text terms for mining title, abstract and keywords using stars (*) as wildcard and/or truncation marks as follows: ("neoplasm*"), ("cancer*"), ("carcin*"), ("tumo*"), ("malign*") and ("oncolog*"). In OVID, we applied the Mesh-term "Diet Therapy," "Ketogenic Diet," "Diet, carbohydrate restricted" or "Low Carbohydrate Diet," thereby combining the controlled vocabulary with appropriate free text terms for mining title, abstract and keywords; in EBSCO, an analogous vocabulary was used. Obtained hits were combined with the vocabulary for cancer mentioned above (Table 1). To limit the final dataset, we only searched for original, peer-reviewed articles. Finally, the search was restricted to "human," "English" and the time frame from January 1980 to October 2016. In total, we obtained 449 articles from the combined search of EMBASE and MEDLINE using OVID and 62 additional hits by mining articles of the databases CINHAL, ERIC, PSYCHINFO and SOCINDEX using EBSCO. Out of 511 articles, 11 duplicates were removed, finally locating 500 hits. In addition, lists of references were screened for relevant publications. The search was limited to clinical studies, case–control and cohort studies, published as full paper in English between January 1980 and October 2016. As guidelines for clinical nutrition in oncology point to the importance of meeting required energy requirements and avoiding malnutrition, the literature search was limited to clinical studies in humans utilizing isocaloric KD dietary regimes [17].

Following the recommendations of the Cochrane Effective Practice and Organization of Care (EPOC) Reviews systematic reviews and meta-analyses, randomized controlled studies (RCT), non-randomized controlled studies, uncontrolled studies (process monitoring, uncontrolled before–after studies and time series analyses) and observational studies were included [18]. Additionally, we decided with respect to the low number of publications on this topic to also include case series and case studies.

Three reviewers (BL, NE and JH) evaluated title and abstract of the articles identified through the database searches independently. Afterward, the full texts of the included articles were reviewed for the final inclusion. In case of differences, a fourth author (AB) made the final decision based on a discussion of all three authors.

The relevant data of the finally included studies were systematically recorded in an evidence table by NE. The table contains study design, study population, type of ketogenic diet and the reported outcomes (see Fig. 1; Table 2).

Results

Evidence from clinical studies

To date, few clinical trials utilizing isocaloric KD regimes as an intervention for cancer patients exist. Table 2 includes an overview of all 15 case reports and clinical studies mined from our search [19–32]. Five are case reports, eight are prospective studies (six single-arm studies, one single-arm crossover study, and one three-arm study utilizing TPN), and two are retrospective studies. No

Table 1 Vocabulary list utilized for systematic search

Vocabulary in OVID	
1	Exp neoplasms/
2	(Neoplasm* or cancer* or carcin* or tumo* or malign* or oncolog*).tw.
3	1 or 2
4	Exp diet therapy/
5	(Ketogen* or low-carb* or carbohydrate-restrict* or atkins).tw.
6	4 and 5
7	Exp ketogenic diet/
8	Exp diet, carbohydrate restricted/
9	Exp low carbohydrate diet/
10	7 or 8 or 9
11	6 or 10
12	3 and 11
13	(Ketogenic and diet).tw
14	(Ketogenic adj3 diet).tw
15	13 or 14
16	(Carbohydrate* adj3 restrict*).tw
17	Atkins-diet*.tw
18	Modified Atkins-diet*.tw
19	Low-glycemic-diet*.tw
20	Triglyceride-diet*.tw
21	Ketogenic-diet*.tw
22	Low carb diet*.tw
23	(Carbohydrate* adj3 restrict*).tw
24	Low-glycemic-diet*.tw
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	3 and 25
27	12 or 26
Vocabulary in EBSCO	
S1	(MH “oncology+”) or DE (“oncology”) or (SU oncology)
S2	(MH “cancer+”) or (DE “cancer”) or (SU “cancer”) or SU (cancer)
S3	(MH “neoplasms+”) or (DE “neoplasms”) or (SU “neoplasms”) or SU (neoplasms)
S4	SU (neoplasm* or cancer* or carcin* or tumo* or malign* or metasta* or oncolog*) or TI (neoplasm* or cancer* or carcin* or tumo* or malign* or metasta* or oncolog*) or AB (neoplasm* or cancer* or carcin* or tumo* or malign* or metasta* or oncolog*)
S5	S1 or S2 or S3 or S4
S6	(MH “restricted diet+”) or (DE “restricted diet”) or (SU restricted diet)
S7	(MH “dietetics+”) or (DE “dietetics”) or (SU dietetics)
S8	(MH “diets+”) or (DE “diets”) or (SU diets)
S9	S6 or S7 or S8
S10	SU (ketogen* or low-carb* or carbohydrate-restrict* or Atkins) or TI (ketogen* or low-carb* or carbohydrate-restrict* or Atkins)or AB (ketogen* or low-carb* or carbohydrate-restrict* or Atkins)
S11	S9 and S10
S12	S5 and S11
S13	(MH “diet, ketogenic+”) or (DE “diet, ketogenic”) or (SU diet, ketogenic)
S14	S5 and S13
S15	(MH “diet, low carbohydrate+”) or (DE “diet, low carbohydrate”) or (SU diet, low carbohydrate)
S16	S5 and S15
S17	S12 or S14 or S16
S18	TI [(ketogen* and diet*)] or AB [(ketogen* and diet*)]
S19	SU (ketogenic-diet*) or TI (ketogenic-diet*) or AB (ketogenic-diet*)

Table 1 continued

S20	SU (ketogenic N3 diet) TI (ketogenic N3 diet) or AB (ketogenic N3 diet)
S21	SU (carbohydrate-restrict*) or TI (carbohydrate-restrict*) or AB (carbohydrate*-restrict*)
S22	SU (carbohydrate* N3 restrict*) or TI (carbohydrate* N3 restrict*) or AB (carbohydrate* N3 restrict*)
S23	TI [(low carb* and diet)] or AB [(low carb* and diet)] or TI [(carbohydrate and restriction)] or AB [(carbohydrate and restriction)]
S24	SU (low carb diet*) or TI (low carb diet*) or AB (low carb diet*)
S25	SU (Atkins-diet*) or TI (Atkins-diet*) or AB (Atkins-diet*)
S26	SU (low-glycemic-diet*) or TI (low-glycemic-diet*) or AB (low-glycemic-diet*)
S27	SU (triglyceride-diet*) or TI (triglyceride-diet*) or AB (triglyceride-diet*)
S28	S18 or S19 or S20
S29	S5 and S28
S30	S17 or S29
S31	S21 or S22 or S23 or S24 or S25 or S26 or S27
S32	S5 and S31
S33	S30 or S32

study with a methodological rigorous design was found. In total, 330 patients have been included. However, only 177 (53%) of these patients followed a ketogenic diet at any point in the duration of the studies. Only 67 of 177 (37% of the patients following the KD—or 20% of all patients included in the studies) managed to adhere to the dietary recommendations for the duration of the study. Duration of the dietary intervention ranges from a single 3-h regime of glucose-based or lipid-based total parenteral solution [26] or, when considering oral diets, anywhere from 4 days to 5½ years (a single case within a retrospective study [25]). The dietary intervention last ≥3 months in only 6 of the 15 studies listed [21, 25, 27, 31–33]. The studies are limited by their sample sizes and lack in homogeneity of type, location and cancer stage, and thus, results cannot be compared. Furthermore, unlike previous studies conducted in the area of epilepsy, the studies in the area of cancer lack consistency and do not utilize clearly comparable and consistent standardized dietary protocols. In some studies, the patient's diet was not supervised by a registered dietitian. Instead, patients were given instructions and a set of brochures with sample recipes and food facts. A few studies provide detailed protocols, which could be replicated in future research; however, as Table 2 makes clear, no two studies seem to utilize the same dietary protocol. Some studies used supportive nutritional therapy in the form of parenteral infusions, which cannot be compared to studies utilizing an oral diet. Furthermore, some studies monitored ketones in blood samples while others measured ketones in the urine—or compared both.

Most studies tested feasibility, patient quality of life and adherence and did not, or could not, evaluate antitumor effects of the KD. Of the studies that reported antitumor observations, non-statistical significance could be derived. Tan and Shalaby observed no correlations between clinical response and ketosis or glycaemia [33]. In contrast, Fine et al. [28] report that the extent of ketosis, but not calorie deficit derived from dietary restriction or weight loss, correlated with stable disease or partial remission based on results from ten patients. In Rossi et al.'s three-arm trial, 9 of the 27 patients received the KD delivered through total parenteral nutrition (TPN). For all 27 patients, including the nine receiving the KD, there was no significant difference in tumor growth between the three arms [17]. Champ et al. retrospectively investigated 53 patients with high-grade glioma treated with concurrent chemoradiotherapy and/or adjuvant chemotherapy. In total, 6 of the 53 patients followed a KD without major complications, but no conclusions regarding survival or tumor growth could be drawn due to the small patient numbers [16]. Schmidt et al. also reported positively with regard to feasibility and quality of life in six patients, but again no conclusions regarding survival or tumor growth could be drawn [18]. Rieger et al. investigated 20 patients with recurrent glioma and concluded that the KD is feasible and safe, but probably has no significant clinical activity when used as single agent [20].

Discussion

Before discussing the use of ketogenic diets for cancer patients, it is necessary to understand the different macronutrient breakdowns of the main forms of the KD. Figure 2 displays the different macronutrient breakdowns of the four main forms of the ketogenic diet that have been

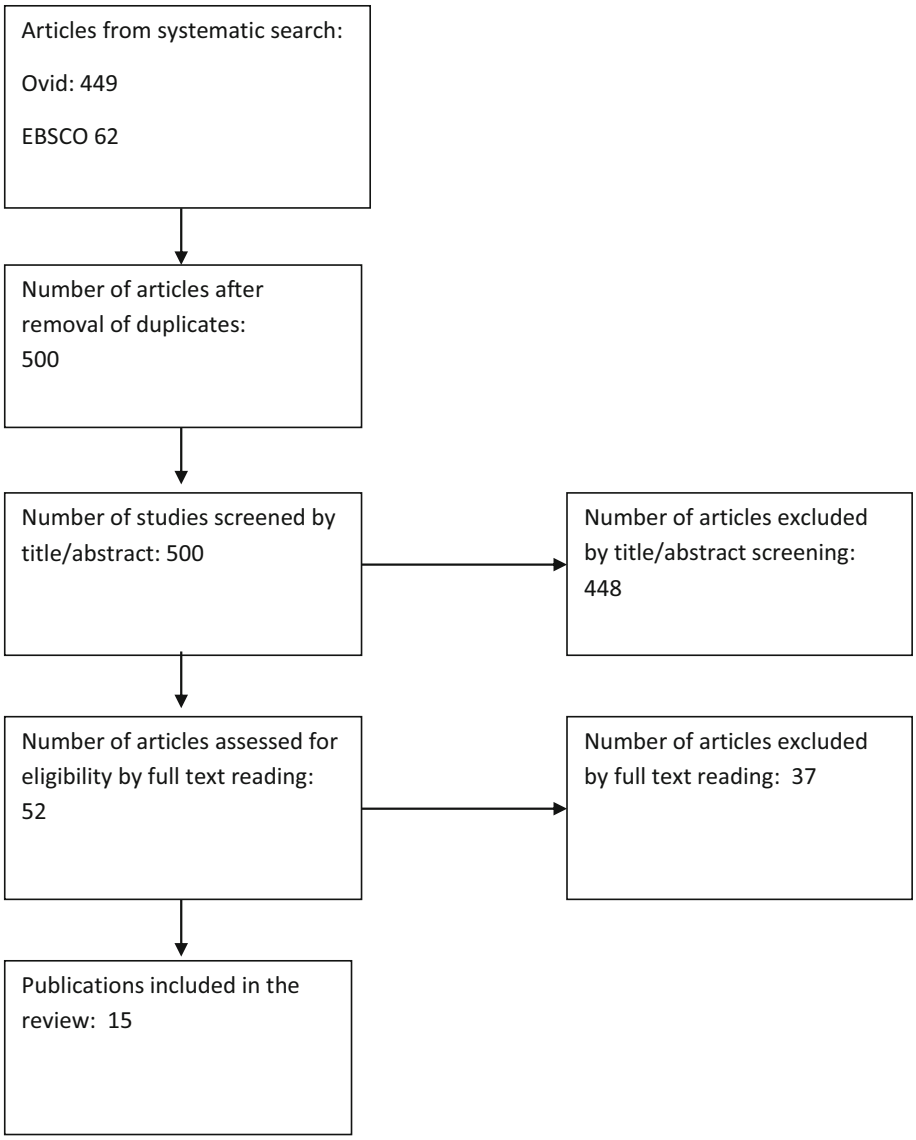

Fig. 1 Study flow diagram

studied using consistent protocols: the classical KD, the middle chain triglyceride diet, (MCT), the low-glycemic index therapy diet (LGIT) and the modified Atkins diet (MAD) [5, 8, 10, 34–36]. All forms of the diet are characterized by fat intake well above recommendations in guidelines for oncology patients which recommend up to 50% of the total energy intake can be derived from fat, but stress that this should not be accompanied by a carbohydrate restriction [17]. Furthermore, for all versions, it is necessary to select high-fat foods as well as additional sources of fat at every meal in order to achieve the recommended fat content. Finally, it is important to know that all forms of the KD are considered nutritionally inadequate. Therefore, the international KD consensus statement and the S1 guidelines require a carbohydrate-free multivitamin with trace minerals (including selenium). Calcium is also required and vitamin D is strongly recommended [5, 35]. Relative contraindications such as cardiomyopathy, and diseases of the liver, kidney and pancreas should be considered closely particularly when considering applying the diet to a cancer patient with comorbidities or medications that may stress these organs (for example, cisplatin regimes). As the long-term application of the KD has been correlated with calcium deficits and the metabolic state of acidosis can exacerbate bone loss, a notable relative contraindication is the presence of osteoporosis or osteopenia which could be important when considering its use among patients with a higher risk of osteoporosis. Similarly, the KD diet can increase incidence of kidney stone formation. Thus, it may not be an appropriate choice for a patient with a history of nephrolithiasis or renal tubular acidosis [5, 34, 35].

The 15 studies identified in this review utilize differing variations of all four versions, with inconsistent and, at

Table 2 Overview of isocaloric ketogenic dietary regimes applied to oncology patients—summary of existing evidence

Authors	Subjects	Subjects on KD	Journal and year	Type	Cancer site	KD dietary intervention	Duration	Dietary adherence % of patients completed diet	Main reported outcome	Relevant clinical parameters and/or side effects
Case reports										
Fearon et al. [19]	$N = 5$	$N = 5$	Am J Clin Nutr, 1988	Case reports	Advanced cancer with severe weight loss 2 = lung 2 = stomach 1 = ovarian	Nasogastric tube: normal diet followed by isonitrogenous, isocaloric, ketogenic diet	13 days total—6-day normal diet and 7 KD	100%	No significant alteration in host nitrogen balance or protein synthesis, degradation or turnover rates	None reported
Nebeling et al. [20]	$N = 2$ female pediatric patients	$N = 2$	J Am Coll Nutr, 1995	Case reports	Two advanced stage malignant astrocytoma tumors	60% MCT oil 10% LCT-based KD	8 weeks	100%	21% Average decline in glucose uptake at tumor site measured with PET scan	Authors do not recommend for patients receiving radiation or chemotherapy and those who have food aversions, kidney and liver problems, nausea or vomiting
Bozetti et al. [21]	$N = 1$	$N = 1$	Clin Nutr, 1996	Single case report	Intra-abdominal desmoid tumor	Home-based TPN: 28 kcal fat/kg/day, 1.5 g protein/kg/day; 40 g glucose/day	5 months	100%	No change to tumor volume	Good tolerance to feeding regime, weight maintained
Branca et al. [22]	$N = 1$	$N = 1$	Anticancer Res., 2015	Single case report	Human epidermal growth factor receptor (HER2)-positive breast cancer	Self-administered KD rich in olive oil and vitamin D3 supplementation (10,000 IU/day)	3-week period between diagnosis and operation	100%	HER2 score reduced from >10% score 2 + *t*0 negative score 0 and progesterone receptor from >1 to 20%	None reported

Table 2 continued

Authors	Subjects	Subjects on KD	Journal and year	Type	Cancer site	KD dietary intervention	Duration	Dietary adherence % of patients completed diet	Main reported outcome	Relevant clinical parameters and/or side effects
Klement and Sweeny [23]	$N = 6$	$N = 6$	BMC Res Notes., 2016	Prospective case reports	$N = 3$ Rectal adenocarcinoma $N = 1$ Lung cancer $N = 1$ Breast cancer $N = 1$ Prostate cancer undergoing radiotherapy	Six followed a self-administered KD regime 50 g CHO/day. Average fat intake was 73% (SD 5%). Ratios varied from 1.8:1 to 0.8:1	Patient dependent from 32 to 73 days	Lack of consistent ketosis indicates either compliance problems or problems with or dietary prescription	KD feasible in ambulatory setting; reduction in fat mass	No adverse diet-related side effects occurred though weight loss reported subjective reports that diet was good
Clinical studies										
Rossi-Fanelli et al. [24]	$N = 27$	$N = 9$	Clin Nutr., 1991	Three-arm prospective crossover study	Tumors of the gastro intestinal tract	(A, B and C) Each (A) glucose-based TPN formula or (B) lipid-based TPN formula or (C) an oral diet isocaloric and isonitrogenous to A and B	14 days	Not relevant due to TPN	No significant change in tumor proliferation	Total lymphocyte count significantly reduced in arms A and B; blood glucose and triglyceride levels in patients given either TPN regime remained within the normal range
Chu-Shore et al. [25]	$N = 5$ Pediatric patients	$N = 5$	Brain Dev., 2010	Retrospective, single-arm pilot study	Tuberous sclerosis complex	Traditional: diet ratio 3:1 ($N = 2$), 3:5:1 ($N = 2$), 4:1 ($N = 1$)	Varied: 3 months–5.5 years	4/5	No significant change in tumor regression and/or suppression	1/5 stopped diet due to reported cognitive changes
Bozzetti et al. [26]	$N = 12$	$N = 12$ on single administration 3-h long regime	Clin Nutr., 2004	Single-arm crossover design prospective study	Colorectal cancer with liver metastases	Single 3-h regime of glucose-based (GTPN) or a lipid-based (LTPN) containing 4 mg glucose/kg/min followed by 2 mg lipid/kg/min, respectively, delivered on separate days	3 h before fluoro-2–deoxy-D-glucose tumor uptake analysis		No substantial stimulation or suppression of FDG uptake by the subsequent administration of GTPN or LTPN	NA

Table 2 continued

Authors	Subjects	Subjects on KD	Journal and year	Type	Cancer site	KD dietary intervention	Duration	Dietary adherence % of patients completed diet	Main reported outcome	Relevant clinical parameters and/or side effects
Schmidt et al. [27]	$N = 16$	$N = 16$	Nutr Metab., 2011	Prospective, single-arm pilot study	Advanced metastatic tumors	KD (less than 70 g CHO per day) with a supply of food additives to prepare a protein/fat shake	3 months	5/16 Ended the study on the diet. Various reasons cited for dropout	Statistical evaluation of the effect of the diet on tumor characteristics and QOL is not statistically feasible	Side effects included ongoing weight loss, temporary constipation and fatigue; implementation and acceptance of the diet varied greatly
Fine et al. [28]	$N = 12$	$N = 10$	Nutrition, 2013	Prospective single-arm pilot study	Incurable, advanced cancer various tumors	KD with a supply of sample products to help adherence	28 days	5/10 Completed 28-day trial	Dietary approach feasible for selected patients with advanced cancer	4% Mean weight loss
Schroeder et al. [29]	$N = 12$	$N = 12$	Nutr Cancer., 2013	Prospective quantitative study	Head and neck cancer	KD diet not described	4-day KD compared to 24-h western diet	No dropout due to no defined begin or end or regime	Decline of mean lactate concentration in the tumor tissue after ketogenic diet	Decreased range of amplitudes of the glucose plasma concentrations with no hypoglycemic episodes
Rieger et al. [30]	$N = 20$	$N = 20$	Int J Oncol., 2014	Prospective, single-arm pilot study	Recurrent glioblastoma	KD (MAD) 60 g CHO/day	6 weeks	3/20 Stopped due to restrictions in QOL and poor tolerability	No significant clinical activity when used as single agent in recurrent glioma	Ketogenic diet safe and relatively well tolerated. Three patients discontinued the diet
Champ et al. [31]	$N = 53$	$N = 6$	J Neuro-oncol., 2014	Retrospective review	High-grade glioma treated with concurrent chemoradiotherapy and adjuvant chemotherapy	6/53 followed self-administered KD $\leq$ g CHO daily	3–12 months	As time varied as to individual adherence, no participants could be considered dropouts	KD safe and well tolerated during the standard treatment of GBM	Weight loss, constipation, fatigue, hypoglycemia, deep vein thrombosis, nephrolithiasis

Table 2 continued

Authors	Subjects	Subjects on KD	Journal and year	Type	Cancer site	KD dietary intervention	Duration	Dietary adherence % of patients completed diet	Main reported outcome	Relevant clinical parameters and/or side effects
Jansen and Walach [32]	$N = 78$	$N = 7$ on Full KD regime	Oncol Lett., 2016	Systematic, prospective cohort study in general practice	Various sights and stages of cancer	KD diet not described in detail except the support of products of a single company	Duration no defined but more than one patient maintained the diet for more than 24 months	Not reported	An observed reduction in TKTL1 score from baseline to the final measurement was associated with ketogenic diet	Number of observations for the majority of the variables reported insufficient to perform a reliable statistical analysis
Tan-Shalaby et al. [33]	$N = 17$	$N = 11$	Nutr Metab., 2016	Single-arm prospective feasibility trial	Various sites of advanced cancer and tumor histology	Modified Atkins diet with 20–40 g of carbohydrates. Restricted consumption of high carbohydrate foods but no restrictions for calories, protein or fats	16 weeks	Only 3/17 patients continued diet past 16 weeks. Dietary compliance reported as difficult	Diet safe and feasible but associated	8/11 73% experienced weight loss. 7/11 (64%) experienced hyperuricemia; various further adverse effects reported
Totals	$N = 330$	177						67/177 Completed diet 18 no data given		

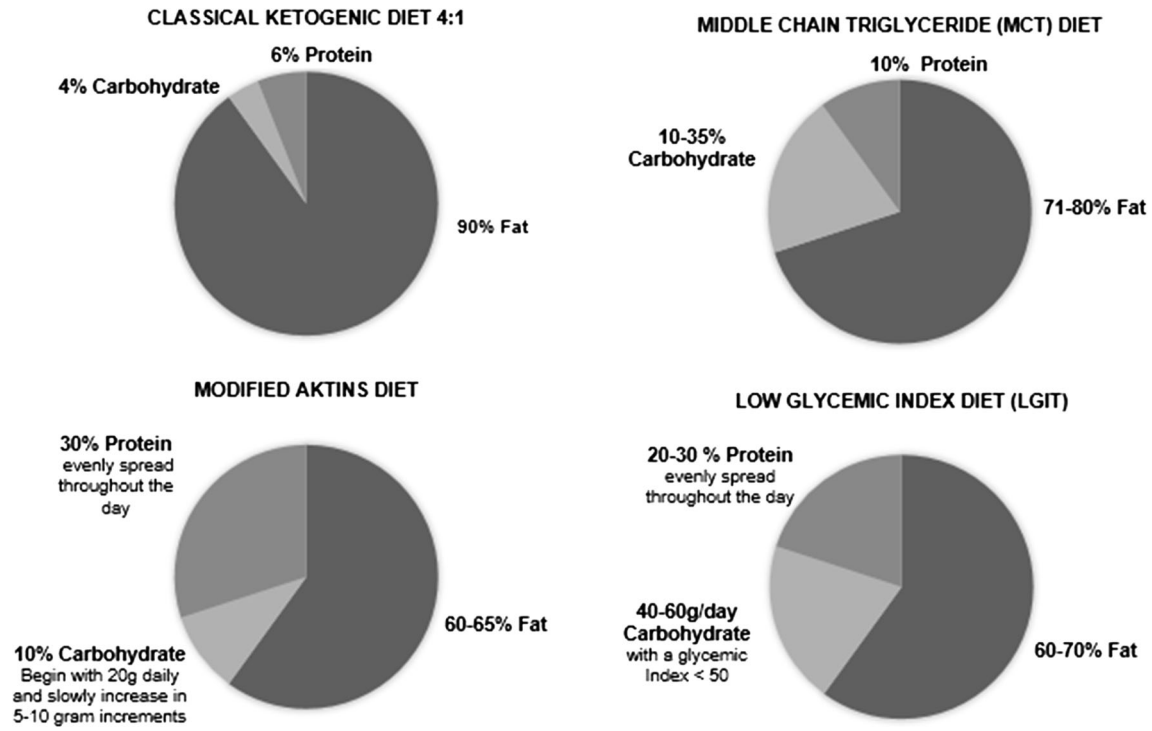

Fig. 2 Macronutrient breakdown of the four major variations of ketogenic diet presented as percentage of total individual estimated energy requirements

times, poorly described protocols. With the exception of Branca et al. [22] who describe supplementing their dietary protocol with 10,000 IU of vitamin D3 daily, no information was provided as to supplementation of any vitamins or minerals. This lack of clear agreement as to dietary protocol further complicates possible points of comparison especially with respect to side effects, quality of life and adherence.

Low adherence by cancer patients even in studies with specialized nutrition counseling also appears to be a problem. The low rate of acceptance of these dietary restrictions points to negative effects on quality of life as described by Rieger et al. [30]. These barriers are similar for both the traditional KD and consistent among its use for intractable epilepsy. In fact, a 2006 meta-analysis of the efficacy of the KD for epilepsy from Henderson et al. [8] that included 19 observational studies with 1084 pediatric patients (mean age at study begin 5.78 $\pm$ 3.43 years) found that 29.6% of the 552 dropouts ended the diet due to restrictiveness and/or dietary side effects. Klein et al. found 2014 even higher rates of diet discontinuation among adults with intractable epilepsy: 51% of patients of the traditional KD and 42% of patients on the MAD stopped the diet before study completion. Most patients, even those with 75–100% seizure frequency reduction, eventually stopped the diet due to restrictiveness and complexity of the diet and also due to social restrictions [37]. In contrast, Neal et al. [38] reported a 15% dropout rate in a closely monitored traditional KD regime and Sharma et al. [39] report an 8% dropout on the MAD. These differences may be due to differing support systems. For cancer patients, it is clear from our data that only 67 of the 177 patients (37%) adhered to their dietary prescription. For 18 patients, no data were discernable. The remaining 75 patients (42%) were not able or willing to comply to the dietary restrictions.

Notably, the possibility of adverse events due to the KD as well as potential increase in symptoms and side effects due to the disease or the conventional cancer therapy (i.e., nausea and changes in appetite) should not be overlooked. Table 3 lists reported side effects from the KD derived from studies among children with seizures and also adult cancer patients as reported in the studies included in this review [5, 10, 20, 23, 25, 27, 28, 31, 33, 35, 40]. Notably, a few reported side effects from studies on the application of the KD to epileptic patients have also been severe enough to be listed in the guidelines as a relative contraindication. Particularly among cancer patients side effects might not be attributed to the dietary regime but mistakenly be thought of as side effects of the therapy or disease progression. Moreover, there are some hints as to an understating of side effects. For example, Klement and Sweeny report no adverse diet-related side effects—although two patients experienced nausea and changes in appetite while

Table 3 Reported adverse effects of KD listed alphabetically

Modified after [5, 10, 20, 23, 25, 27, 28, 31, 33, 35, 40]
Anemia
Amino acid levels: decreased
Acidosis (esp. due to dehydration)
Dehydration/lack of thirst
Cardiac abnormalities (e.g., cardiomyopathy)
Functional changes in basal ganglia, granulocytes and thrombocytes
Flu-like symptoms/fatigue
Gastrointestinal symptoms (including: abdominal pain, constipation, diarrhea, reflux, vomiting)
Halitosis
Hypercholesterolemia
Hyperuricemia
Hypocalcemia
Hypoglycemia
Hypo- and Hyperkalemia
Hyperlipidemia
Hypomagnesemia
Optic neuropathy
Pancreatitis
Pedal edema
Pruritus
Renal calculi
Weight loss
Additional reported adverse effects from long-term adherence (>6 months)
Arteriosclerosis
Carnitine deficiency
Fatigue/sedation
Irregular menses
Osteopenia, osteoporosis, and bone fractures
Decreased growth in children and adolescents
Vitamin, mineral, and enzyme deficiencies

one experienced diarrhea by the end of the trial [23]. In contrast, Nebeling et al. [20] acknowledge the side effects and do not recommend the KD for patients receiving radiation or chemotherapy and those who have food aversions, kidney and liver problems, nausea or vomiting.

As cancer patients are particularly susceptible to clinical significant malnutrition in the form of weight loss from both fat and muscle mass, this side effect should be most carefully evaluated before applying the diet in clinical settings. Tan and Shalaby report a weight loss in 73% of participants although the caloric intake was not restricted. In fact, they observe mean weight loss of 1.5 kg after only 2–3 days of dieting, and by the end of the study the mean weight loss for all subjects was 7.5 ± 5.8 kg [33]. Fine et al. [28] were aiming for an isocaloric dietary intervention, yet they observe a mean 35% caloric deficit and a 4% weight loss leading them to raise the question of whether caloric restriction played a role in their findings.

Conclusion

In contrast, to the considerable attention from researchers, physicians and the media for its potential role in cancer treatments, evidence on benefits regarding tumor development and progression as well as reduction in side effects of cancer therapy is missing. More robust and consistent clinical evidence investigating comparable patient groups with comparable methodology, dietary protocols and consistent results are warranted before the KD can be recommended for any single cancer diagnosis or as an adjunct therapy. Randomized trials with a well-designed control

group should be the preferred study type and possible side effects including weight loss must be carefully weighed when considering applying the diet to cancer patients.

Compliance with ethical standards

Conflict of interest Nicole Erickson has received a speaker honorarium from B. Braun, CSL-Behring and Fresenius Kabi. The content of these talks was not related to the content of this article. A. Boscheri, B. Linke and J. Huebner declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors and therefore did not require ethical approval.

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