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REVIEW ARTICLE

Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes

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Abstract
Preclinical data provide evidence for synergism between ketogenic diets (KDs) and other oncological therapies. The aim of this systematic review was to summarize data from clinical studies that have tested KDs along with other treatments used within medical oncology. The PubMed database was searched using the key words "ketogenic" AND ("cancer" OR "glioblastoma"). A secondary search was conducted by screening the reference lists of relevant articles on this topic. Relevant studies for this review were defined as studies in which KDs were used complementary to surgery, radio-, chemo-, or targeted therapy and at least one of the following four outcomes were reported: (i) Overall survival (OS); (ii) progression-free survival (PFS); (iii) local control rate; (iv) body composition changes. Twelve papers reporting on 13 clinical studies were identified. Nine studies were prospective and six had a control group, but only two were randomized. KD prescription varied widely between studies and was described only rudimentarily in most papers. Adverse events attributed to the diet were rare and only minor (grade 1–2) except for one possibly diet-related grade 4 event. Studies reporting body composition changes found beneficial effects of KDs in both overweight and frail patient populations. Beneficial effects of KDs on OS and/or PFS were found in four studies including one randomized controlled trial. Studies in high-grade glioma patients were not sufficiently powered to prove efficacy. Evidence for beneficial effects of KDs during cancer therapy is accumulating, but more high-quality studies are needed to assess the overall strength of evidence.

Keywords Cancer · Evidence · High-grade glioma · Ketone bodies · Metabolic therapy · Skepticism

Introduction

During the last century, surgery, ionizing radiation, and chemotherapeutic drugs emerged as the three main pillars of cancer treatment and—now complemented by targeted inhibitors of oncogenic pathways and immune checkpoints—still constitute the standard treatments within modern medical oncology. Frequently, however, the efficacy of these treatments comes at the expense of significant side effects. These side effects narrow the therapeutic window, meaning that the dose of radiation or chemotherapy has to be limited, or surgical margins reduced, in order to limit their normal tissue complication probability. This in turn also lowers the probability of tumor control. It is therefore important to search for additional, complementary treatments that widen the therapeutic window. As one such complementary treatment, metabolic therapy in the form of a ketogenic diet (KD) has been proposed. A KD is defined as a high-fat, low-carbohydrate diet that mimics fasting metabolism with the main characteristic of serum ketone body concentrations in a higher physiological range (typically 0.5–4 mmol/l). Historically, the so-called classic KD has been adopted as a treatment for pediatric epilepsy from the 1920s being based on a 4:1 or even more extreme weight ratio between fats and the sum of carbohydrates and protein also known as the ketogenic ratio. The equal weighting of carbohydrates and protein as anti-ketogenic is thereby known to be inaccurate, since protein does consist of specific ketogenic and anti-ketogenic amino acids [1]. Modern forms of KDs are not as protein (and even carbohydrate) restrictive as the classic version, in particular when supplemented with ketogenic medium chain triglycerides (MCTs). Such modern versions

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include the modified Atkins diet and MCT-based KD [2], Paleolithic KD [3], or Mediterranean KD [4].

Preclinical data have not provided unequivocal evidence for anti-tumor effects of KDs when applied as a monotherapy—the efficacy appears to vary between tumor models and depend on factors such as the timing of diet initiation relative to tumorigenesis [5–7]. In contrast, there is a much stronger evidence base for synergism between KDs and other oncological therapies. For example, KDs have been shown to inhibit glycolysis and increase oxidative stress in cancer cells, in this way enhancing the effects of therapies that act via the production of reactive oxygen species such as hyperbaric oxygen, radiotherapy, and many chemotherapeutic drugs (reviewed in [8–11]). A KD has also been shown to support targeted therapy by PI3K inhibitors through its ability to suppress insulin feedback caused by reactive hyperglycemia after PI3K inhibition [12].

The evidence for anti-cancer effects of KDs from preclinical data has been paralleled by a growing interest in their clinical application from both patients and physicians. For example, in a survey of high-grade glioma patients, almost three quarters of patients displayed their willingness to try a modified Atkins diet for 3 months [13]. Furthermore, in a survey of 68 naturopathic physicians, KDs were the fifth most frequently recommended dietary intervention for pediatric oncology patients [14].

Until recently, however, actual clinical research on KDs and cancer was mostly limited to small pilot studies or case reports [15–21]. The lack of studies occupying higher levels in typical "evidence hierarchies"[1] has been emphasized by some authors [24–26], discouraging the clinical application of KDs by confusing absence of evidence for efficacy with evidence for absence of efficacy [27, 28]. We will call this discouragement of KDs based on the lack of high-quality studies *methodological skepticism.* Some authors also express a second, more fundamental form of skepticism that we will call *fundamentalist skepticism.*[2] A characteristic of fundamentalist skeptics is the explicit warning against consuming a KD during cancer therapy despite a lack of data supporting such claims [27, 31].

In this systematic review, our aim is to address both types of skepticism by focusing on data from clinical studies that have tested a KD within the context of medical oncological treatments. Indeed, results from randomized and non-randomized controlled trials on KDs in cancer patients are accumulating and with them data about the safety of KDs in various patient populations. Also, clinically relevant endpoints such as overall and progression-free survival have been evaluated by some studies. Reviewing the clinical data, we will conclude that KDs are safe and potentially effective as complementary therapies, but will also discuss the limitations of the published studies and derive some recommendations for future research.

Materials and methods

This systematic review was designed according to PRISMA recommendations [32], but not prospectively registered. We primarily searched the PubMed database using the keywords "ketogenic" AND ("cancer" OR "glioblastoma") on October 24th 2019. Relevant studies for this review were defined as studies conducted within a clinical setting in which KDs were used complementary to surgery, radio-, chemo-, or targeted therapy and at least one of the following four outcomes were reported: (i) Overall survival (OS); (ii) progression-free survival (PFS); (iii) local control rate (LCR); (iv) body composition changes. Reviews, case reports, and case series were excluded, but their reference lists were searched for additional relevant studies.

From the relevant studies, the following information was extracted: Study type (controlled/ uncontrolled) and design (prospective/ retrospective), number of patients, treatment regime, follow-up time, outcome measure, KD prescription, involvement of a dietitian (yes/no), and number and severity of side effects attributed to the KD.

Results

The primary literature search in PubMed yielded 259 results (Fig. 1). After excluding non-relevant studies, a total of 11 original articles were included [13, 33–42]. Another clinical study from Japan published as a conference abstract [43] and full paper [44] was found through the secondary search. It had been published in Japanese and was translated into German via Google translate (https://translate.google.com/).

Table 1 lists the included studies with information about the studied outcomes, while Table 2 provides details on the KD prescription and diet-related side effects.

[1] The general problems with evidence hierarchies have been thoroughly discussed. For examples see Stegenga [22] or Klement and Bandyopadhyay [23].

[2] These two types of skepticism parallel those identified by the astronomer–philosopher Milan Ćirković regarding SETI, the search for extra-terrestrial intelligence in the Universe:"instrumentalist" (or methodological) and "fundamentalist" skepticism [29]. Indeed we argue that certain parallels can be drawn between SETI, where dogmatic principles, religious or otherwise dictate an individual's attitude towards the endeavor, and nutrition research which is often confounded with pseudo-scientific beliefs, conflicts of interest, and dogmatism [30].

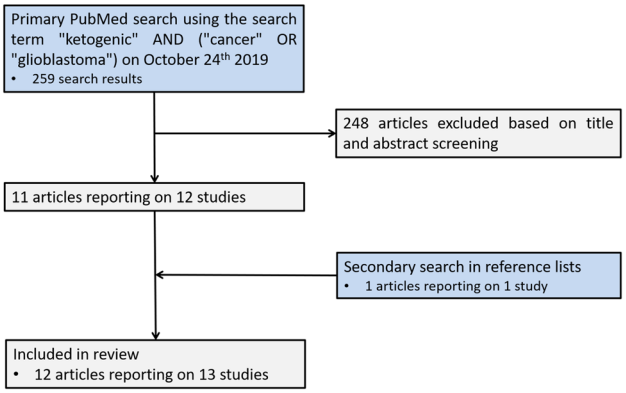

Fig. 1 PRISMA [32] flow chart displaying the study selection procedure for this systematic review

General study characteristics

The twelve included articles reported on 13 individual studies. Of these, nine (69%) were prospective and six (46%) had a control group, but only two of those were randomized (Table 1). The majority of the studies focused on cancers with a poor prognosis: high-grade gliomas and pancreatic and metastasized cancers. Of the six controlled studies, four investigated body composition changes, but only one evaluated OS, two evaluated PFS, and none LCR.

KD prescription varied widely between studies and was described only rudimentary in most papers (Table 2). A detailed description of the actually consumed macronutrient and micronutrient content of the diets was missing in all papers. A dietitian was involved in 11 of the 13 studies. The methodology of assessing ketone body levels and therefore diet compliance varied widely, with three studies only using urinary ketone measurements [13, 33, 37]. The definition of the ketosis threshold also varied across studies, ranging from 0.3 mmol/l [42] to 0.6 mmol/l [35]. Adverse events attributed to the diet were rare and only minor (grade 1–2) except for one possibly diet-related grade 4 hyperuricemia occurring in the ketolung study [35].

In the following, we provide a brief description of important study results according to tumor types.

Neurologic cancers

High-grade glioma patients consuming a KD were investigated in four studies. The ERGO trial by Rieger et al. [33] initially included 20 patients with recurrent glioblastoma who should consume a KD over 6–8 weeks with no simultaneous treatment until clinical evaluation of tumor status. In case of progression, patients were allowed to stay on the diet while receiving salvage therapy. Seven patients continued the KD while receiving bevacizumab alone ($n=4$) or in combination with irinotecan ($n=3$) and were compared to 28 patients receiving bevacizumab within the same time period in the same institution, but not on a KD. Median PFS from bevacizumab initiation was 20.1 weeks (range 12–124 weeks) in the KD group and 16.1 weeks (4–90 + weeks) in the control group which was not statistically different ($p=0.38$).

Two trials administered a KD concurrent with radiochemotherapy to high-grade glioma patients. Woodhouse et al. [34] studied 29 patients on a Modified Atkins Diet (MAD) while receiving 75 mg/m^2 temozolomide and a radiation dose of 59.4 Gy in 30 fractions. Tumor progression was evaluated six months after completion of radiotherapy on MRI scans. This study found a non-significant correlation between having serum β-hydroxybutyrate levels > 1 mmol/l and pseudoprogression of the tumor which was rated as possible radiation sensitization. Two-year OS of 15 glioblastoma patients was 26.7% (4/15); it was 50% (2/4) and 22% (2/9) for those with methylated and unmethylated MGMG status, respectively. These numbers were comparable or somewhat higher than those reported in the literature for other patients having received the same radiochemotherapy protocol. In contrast, nine relatively young glioblastoma patients with good performance status treated with adjuvant standard radiochemotherapy in a trial from the Netherlands experienced a median OS of only 12.8 months (range 9.8–19 months), which is lower than expected from the literature data [39]. Klement et al. hypothesized that this disappointing result may, at least in part, have been due to the highly artificial nature of the KD that was administered over the six weeks of radiochemotherapy [45].

Finally, a feasibility study of a Modified Atkins Diet in six high-grade glioma patients reported body composition changes [13]. Four patients finished the 12-week study period with simultaneous chemotherapy or radiochemotherapy. In these, average weight loss was 1 kg ($p=0.71$) and there was an increase in mid arm muscle circumference of 4.3 cm ($p=0.176$).

Gastrointestinal cancers

A prospective clinical trial from Japan tested the effects of KD in stage IV rectal cancer patients receiving folic acid and fluorouracil-based chemotherapy (FOLFIRI/ FOLFOX) on response rates after one year. The KD group comprised of 10 patients who exhibited an overall response rate of 60% (5 complete remissions, 1 partial response, 1 stable disease case, and 3 progressive disease cases) compared to 21% in 14 control group patients (0 complete responses, 3 partial responses, 6 stable disease cases, and 5 progressive disease cases). This difference in response rates is associated with a p value of 0.0205 in Fisher's exact test and therefore indicates a synergistic effect between the KD and chemotherapy.

Table 1 Overview of studies on the ketogenic diet (KD) in cancer patients and their designs

Study	Year	Tumor	Type	Controlled	Randomized	N_{KD_ini}	N_{Ctr_ini}	N_{KD_fin}	N_{Ctr_fin}	OS	LCR	PFF	Body composition	Simultaneous therapy
Rieger [33]	2014	Glioma	Pro	Yes	No	7	28	7	28	No	No	Yes	No	TT (bevacizumab) + CT in 3 KD patients (irinotecan)
Zahra [35]	2017	Pancreas	Pro	No	No	2	0	1	0	Yes	Yes	Yes	No	CT (gemcitabine) + RT (28 × 1.8 Gy)
		Lung	Pro	No	No	7	0	2	0	Yes	Yes	Yes	No	CT (carboplatin + paclitaxel) + RT (33 × 2 Gy)
Cohen [36]	2018	Ovarian; Endometrial	Pro	Yes	Yes	37	36	25	20	No	No	No	Yes	CT in 4 Ctr patients and 7 KD patients (NA)
Furukawa [43, 44]	2018	Rectal	Retro	Yes	No	10	14	7	13	No	No	Yes	No	CT (FOLFIRI/FOLFOX/trifluridine/TS-1/capecitabine/UFT/UZEL), TT (bevacizumab/panitumumab/cetuximab)
Martin-McGill [13]	2018	Glioma	Pro	No	No	6	0	4	0	No	No	No	Yes	CT (lomustine/temozolomide) + RT in 3 patients
Ok [37]	2018	Pancreas	Pro	Yes	No	20	10	10	9	No	No	No	Yes	NA
Iyikesici [40]	2019	Lung	Retro	No	No	44	0	42	0	Yes	No	Yes	No	CT (carboplatin + paclitaxel), Hyperthermia (60 min, 110 W, > 43 °C) HBO (60 min, 1.5 atmospheres)
Iyikesici [41]	2019	Pancreas	Retro	No	No	25	0	25	0	Yes	No	Yes	No	CT (gemcitabine/FOLFIRINOX), Hyperthermia (60 min, 110 W/130 W, > 43 °C) HBO (60 min, 1.5 atmospheres)
Khodabakhshi [42]	2019	Breast	Pro	Yes	Yes	40	37	30	30	Yes	No	No	Yes	CT (NA)
Klement [38]	2019	Breast, HNSCC, Rectal	Pro	Yes	No	22	63	20	61	No	No	No	Yes	RT (standard fractionation regimes depending on tumor site), CT in 8 rectal KD patients and 21 rectal Ctr patients (capecitabine), 3 HNSCC KD patients and 10 HNSCC Ctr patients (cisplatin)
van der Louw [39]	2019	Glioma	Pro	No	No	9	0	6	0	Yes	No	No	No	CT (temozolomide) + RT (30 × 2 Gy)
Woodhouse [34]	2019	Glioma	Retro	No	No	29	0	28	0	Yes	No	Yes	No	CT (temozolomide) + RT (30 × 2 Gy)

CT chemotherapy, *Ctr* control, *HBO* hyperbaric oxygen, *HNSCC* head and neck squamous cell carcinoma, *LCR* local control rate, N_{Ctr_ini} number of patients initially assigned to the Ctr group, N_{Ctr_fin} number of patients in Ctr group finishing the study, N_{KD_ini} Number of patients initially assigned to KD group, N_{KD_fin} number of patients in KD group finishing the study, *OS* overall survival, *PFS* progression-free survival, *Pro* prospective, *Retro* retrospective, *RT* radiotherapy, *TT* targeted therapy

Table 2 Overview of studies on the ketogenic diet (KD) in cancer patients, their diet prescriptions, and diet-related adverse events

Study	Year	Tumor	Duration	Blood ketone concentration	KD	MCT	Formula	CR	Dietitian	Adverse events (number of patients)
Rieger [33]	2014	Glioma	12–16 weeks	NA (only urinary ketones)	Max. 60 g carbs/day, plant oils, yogurt drink, recipes, info brochures	NA	No	No	NA	Grade 1 diarrhea (NA) and constipation (NA)
Zahra [35]	2017	Pancreas	5 weeks	≥0.6 mmol/l	4:1 ratio (90% fat, 2% carbs, 8% protein), KetoCal breakfast	NA	Yes	No	Yes	None > grade 1–2
		Lung	6 weeks	≥0.6 mmol/l		NA	Yes	No	Yes	Grade 4 hyperuricemia (1)
Cohen [36]	2018	Ovarian; Endometrial	12 weeks	Mean: 0.91 ± 0.16 mmol/l after 12 weeks	70% fat, 5% carbs, 20% protein	NA	No	No	Yes	Minor side effects (NA)
Furukawa [43, 44]	2018	Rectal	1 year	Mean: 0.78 ± 0.407 mmol/l after 3 months, 1 mmol/l after 9 months	1.4:1 ratio, 1.2–1.6 g protein/kg BW, 60-80 g MCT/day	Yes	No	No	Yes	Diarrhea (1) (grade unknown)
Martin-McGill [13]	2018	Glioma	12 weeks	NA (only urinary ketones ≥ 4 mmol/l)	70% fat, max 20 g carbs/day	NA	No	No	Yes	Grade 1 constipation (2)
Ok [37]	2018	Pancreas		NA (only urinary ketones)	70–80% fat, 1 g protein/kg BW	No	No	No	Yes	None
Iyikesici [40]	2019	Lung	NA	NA	Low carb high fat, training, food list	NA	NA	NA	Yes	None
Iyikesici [41]	2019	Pancreas	NA	NA	Low carb high fat, training, food list	NA	NA	NA	Yes	None
Khodabakhshi [42]	2019	Breast	3 months	Mean: 0.917 ± 0.571 mmol/l at third visit, 0.923 ± 0.699 mmol/l at last visit	55% fat, 20% MCT, 19% protein, 6% carbs	Yes	No	No	Yes	None
Klement [38]	2019	Breast, HNSCC, Rectal	4–6 weeks	Median: 0.7 (range 0.12–2.1) mmol/l (rectal), 0.9 (0.05–4.2) mmol/l (HNSCC), 0.71 (0.02–2.59) mmol/l (breast)	75–80%fat Food list, recipes	Some	Some	NA	Yes	None
van der Louw [39]	2019	Glioma	14 weeks	Mean: 4.3 ± 1.2 mmol/l (liquid KD) Mean: 2.9 ± 1.17 mmol/l (solid KD)	Liquid 4:1 KD (8 weeks): 2400 kcal, 49 g protein (8.2%), 11 g carbs (2.0%), 237 g fat (88.8% energy) Solid KD + MCT (6 weeks): 2835 kcal, 54 g protein (7.6%), 57 g carbs (8.0%), 266 g fat (84.4% energy)	Yes	Yes	No	No	Only grade 1: constipation (7), hypercholesterolemia (1), hypoglycemia (1), low carnitine (1), diarrhea (1)
Woodhouse [34]	2019	Glioma	6 weeks	Mean: 1.3 mmol/l	Modified Atkins, 0.8–1:1 ratio	NA	No	NA	Yes	Grade 2 constipation (1)

The "ratio" refers to the ketogenic ratio

BW body weight, *Carbs* carbohydrates, *CR* calorie restriction, *HNSCC* head and neck squamous cell carcinoma, *MCT* medium chain triglycerides

Three studies evaluated the effects of a KD in pancreatic cancer patients receiving other oncological therapies. Zahra et al. [35] reported the final results of the ketopan study, a phase 1 trial in which patients were supposed to consume a 4:1 KD during radiochemotherapy with 600 mg/m^2 gemcitabine and 28 × 1.8 Gy radiotherapy. Only two patients were recruited of which one stopped the KD early after experiencing grade 3 dehydration. The patient who stayed on the KD lost 6.9 kg body weight during radiochemotherapy, while the one who did not stay lost 9.4 kg. Both patients died after 2 and 10 months, respectively.

A Korean study randomized patients who underwent pancreatectomy to a post-surgery KD ($n = 20$) or control diet ($n = 10$) [37]. While 6 patients in the KD group refused to eat the diet and 4 dropped out for other reasons, those that stayed on the diet had a better retention of body cell mass ($p = 0.049$) and skeletal muscle mass ($p = 0.054$) than patients on the control diet until the first outpatient visit.

Finally, Iyikesici presented a retrospective analysis of 25 metastatic pancreatic ductal carcinoma patients who had been treated with gemcitabine or FOLFIRINOX chemotherapy administration in a hypoglycemic state complemented by a KD, hyperbaric oxygen, and hyperthermia [41]. This multimodal treatment resulted in median OS and PFS of 15.8 (95% CI 10.5–21.1) and 12.9 (95% CI 11.2–14.6) months, respectively. These outcomes were at least as good or even better than outcomes for similar patient cohorts treated with a combination of chemotherapy and hyperthermia only [41].

Gynecological cancer

A total of three studies reported outcomes for women with gynecological cancers. Cohen et al. [36] were the first to publish results of a RCT on the KD in cancer patients. Their cohort was composed of 31 patients on a KD of which 25 completed the 12-week study duration and 26 patients were on a low-fat, high-fiber diet recommended by the American Cancer Society of which 20 completed the study. Most women had either endometrial or ovarian cancer in stages I-III, with only one patient in each treatment group having stage IV ovarian cancer. A larger percentage of patients in the KD group had received concurrent chemotherapy compared to the control (28% versus 20%, $p > 0.05$). The main outcome of this analysis was body composition. After 12 weeks, women on a KD had significantly less total body fat, android fat, and visceral fat mass after adjustment for the baseline values; in addition, relative visceral fat mass dropped significantly more in the KD group compared to the control group (−21.2% vs −4.6%). Adjusted lean mass, however, did not differ significantly between both groups at the end of the intervention. Further analyses of the data collected within this study revealed significantly lower fasting serum insulin and C-peptide levels in the KD group at 12 weeks ($p < 0.01$) [36] with no adverse effects on blood lipids [46] as well as higher physical function scores in the KD group [47].

Favorable effects of KD on body composition were also found for early and advanced stage breast cancer patients. In an interim analysis of the ongoing KETOCOMP study [38], a total of seven early stage breast cancer patients eating a KD supplemented with essential amino acids were compared to 22 control patients on an unspecified standard diet during adjuvant radiotherapy. Consuming the KD diet was significantly associated with a gradual body weight (−0.3 kg/week) and fat mass (−0.4 kg/week) reduction, while fat-free mass increased non-significantly by 0.1 kg/week.

A RCT from Iran administered a KD during 3 months to locally advanced and metastatic breast cancer patients undergoing chemotherapy [42]. This study found similar results to the KETOCOMP study in that fat mass and body weight decreased to a much greater extent in the KD group. Furthermore, among patients receiving neoadjuvant chemotherapy for locally advanced breast cancer, OS was longer in the KD than in the control group after 30 months follow-up for neoadjuvant (Fig. 2), but not metastasized patients (Fig. 3); the former difference was associated with a p value < 0.05.

Other cancers

Iyikesici has retrospectively evaluated the response rates and OS of 44 metastatic non-small cell lung cancer (NSCLC) patients that had been treated with weekly carboplatin/paclitaxel in a hypoglycemic state combined with a KD, hyperbaric oxygen, and hyperthermia [40]. Forty-two of the 44 patients were able to complete eight cycles of treatment with almost 100% dose intensity and no side effects related to the complementary treatments. Mean OS and PFS were 42.9 months (95% CI 34.0–51.8 months) and 41 months (31.1–50.9 months), respectively. Despite a large percentage of patients having unfavorable prognostic factors (40.9% brain metastases, 81.8% ECOG performance status ≥ 2), these figures were 4–7 times (OS) and 6–13 times (PFS) larger than the literature values from NSCLC patients who had been treated with a carboplatin/paclitaxel combination.

Finally, head and neck squamous cell carcinoma (HNSCC) patients undergoing radiotherapy ± chemotherapy were included in the KETOCOMP study by Klement et al. [38]. The interim analysis compared five patients on a KD with 17 control patients and found a significant association of KD with retention of body weight ($p = 0.008$), fat-free mass ($p = 0.034$),and skeletal muscle mass ($p = 0.004$).

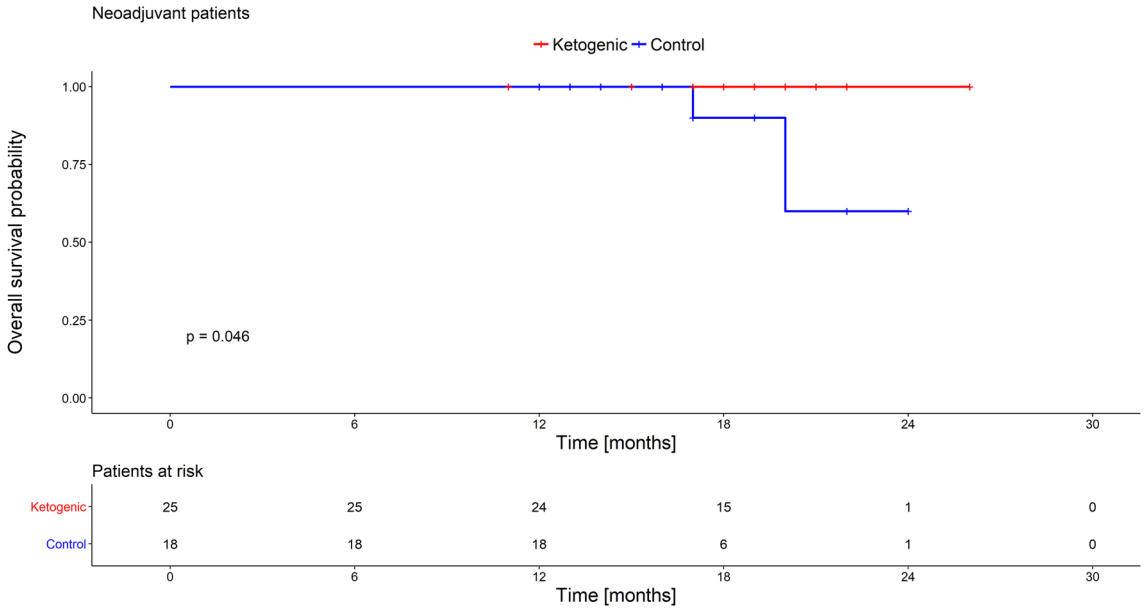

Fig. 2 Kaplan–Meier survival curves for breast cancer patients receiving neoadjuvant chemotherapy ± a ketogenic diet from the study by Khodabakhshi et al. [42]. Based on the individual patient data kindly provided by the authors

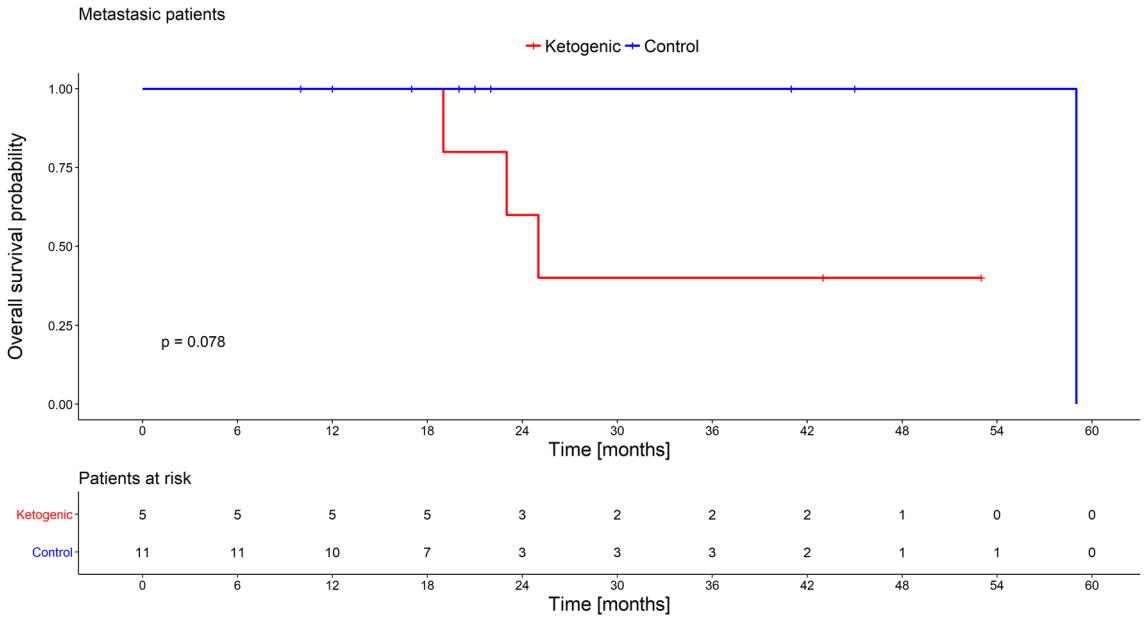

Fig. 3 Kaplan–Meier survival curves for metastasized breast cancer patients receiving chemotherapy ± a ketogenic diet from the study by Khodabakhshi et al. [42]. Based on the individual patient data kindly provided by the authors

Discussion

The aim of this review was to address skepticism about using KDs as complementary cancer treatment strategies in medical oncology by systematically investigating clinical studies from the perspective of their clinical relevance, in particular concerning meaningful endpoints. A total of 13 individual studies reporting at least one of such endpoints were identified and summarized. What is noteworthy is that only two of these studies had an a priori published study protocol [48, 49]. For better reproducibility and description of study procedures, future studies should publish their protocols before the main analyses

are conducted. Furthermore, we would propose more uniformity in measuring ketone body levels and defining ketosis as an indicator of dietary compliance. Urinary ketone measurements in particular, while useful for self-monitoring of patients, cannot be recommended for assessing ketosis since they can produce false-positive results, especially when used during daytime [50]. Ideally, ketone levels should be measured in blood or serum daily or at least once per week. We also propose to define a uniform threshold of ketosis as 0.5 mmol/l β-hydroxybutyrate in accordance with Volek and Phinney [51].

The majority of studies included in this review suffered from different sources of bias: small sample sizes (9 studies had ≤ 10 patients in the KD group for a given patient population), lack of a control group, or lack of randomization giving rise to self-selection, allocation, and performance bias [52]. However, since patients cannot be "blinded" towards the administration of KD and must be willing to change their diet, performance bias, i.e., the expectation of participants towards their treatment, can hardly be ruled out in any nutritional study design. Also, among the 13 studies, two were RCTs showing clinical benefits. Thus, considering that KDs are a relatively new approach for cancer patients,[3] there is no longer a basis for methodological skepticism. We further argue that the nature of complex interventions such as a KD requires a mixture of different study types since each study type has to counterbalance high internal validity (low risk of bias) with extrapolation of findings to the clinical setting (realistic contexts) [7, 54, 55]. In reality, a KD cannot be prescribed to every patient. Instead, many patients often present intrinsically motivated to start a KD. To investigate which factors are associated with a motivation to follow a KD during cancer therapy could be the goal of future studies. Such an investigation has already been performed for fasting (also a ketogenic intervention) during chemotherapy and revealed that patients were motivated to fast mainly to reduce the side effects of chemotherapy and used fasting as an active coping strategy that helped to reduce anxiety [56].

A problem related to extrapolation of study results to clinical reality is the administration of extreme and/or highly artificial diets that have been used in some studies [35, 39]. Notably, these studies have uniformly failed to show any hints for the clinical benefits of their KDs. Problems associated with extreme and/or artificial diets include a lack of micronutrients and phytochemicals [45] and ingestion of problematic molecules such as hydrogenated oils [57]. Furthermore, self-motivated patients in reality will likely buy real foods and cook for themselves, questioning the external validity of studies utilizing extreme and/or artificial diets. To address this problem of external validity, future studies should use diets that are more applicable to the target patient population, e.g., through inclusion of regional foods and consultation of popular KD books. Adherence to a KD can be monitored with ketone body measurements, so artificial diets are not a necessity and should be reserved for those incapable or unwilling to cook for themselves or relying on formula foods due to swallowing difficulties [58]. Anyway, a detailed description of the KD interventions and the estimated macronutrient and micronutrient intake should be presented in the results section of future study papers.

The evidence from the studies summarized in this review points towards beneficial effects of KDs on body composition. This appears to be the case for both overweight patients who benefit by losing body weight and fat mass while maintaining fat-free mass [36, 38] as well as patients at risk for excessive weight and lean mass loss such as head and neck cancer patients undergoing radiochemotherapy [38] or pancreatic cancer patients [37]. The positive effects on body composition are consistent with anti-catabolic effects of ketone bodies in skeletal muscle. Rat studies have shown that ketone bodies inhibit oxidation of the branched chain amino acids [59] and decrease the release of the gluconeogenic amino acid alanine [60] from skeletal muscle. In normal weight and obese subjects, β-hydroxybutyrate infusion lowered plasma alanine levels in the postabsorptive state and attenuated nitrogen excretion by about 30% during prolonged starvation in the obese subjects [61]. Another study in healthy subjects showed that β-hydroxybutyrate infusion decreased leucine oxidation by 30% on average while increasing leucine incorporation into skeletal muscle by 10% [62]. Finally, β-hydroxybutyrate infusion up to 3.5 mM diminished muscle and whole body protein catabolism during an LPS-stimulated acute inflammatory response, evidenced by a > 70% reduction in net forearm phenylalanine release [63]. The latter study may also have translational relevance for inflammation-induced cancer cachexia [64]. In fact, one of the earliest studies on the KD and cancer by Fearon et al. [15] had shown that one week administration of a MCT-enriched KD was able to achieve about 2 kg weight gain and improve performance scores in five severely cachectic cancer patients. An anti-cachectic effect of ketone bodies or a KD is supported by preclinical models of colon adenocarcinoma [65] and pancreatic cancer [66]; in the latter study, β-hydroxybutyrate-mediated inhibition of the cachectic phenotype in vitro and in vivo was related to a downregulation of glycolysis in cancer cells [66]. In this respect, it is interesting that in rats bearing the Walker 256 carcinosarcoma, a high-MCT KD was associated with abnormally high blood glucose levels and—possibly therefore—were unable to counter cachexia [67]. Furthermore,

[3] This statement is not strictly exact since the first clinical study applying a KD in cancer patients was published in 1941 and received a lot of newspaper attention. See Klement [53] for a historical review.

in mice bearing xenografted renal cell carcinomas, a KD induced inflammatory cytokine expression in mouse livers and rapid weight loss, resembling Stauffer's syndrome in renal cell carcinoma patients [68]. Thus, although the available clinical data thus far indicate the safety of KDs and their beneficial effects on body composition, there may be some frail patient populations in which a KD may have negative effects.

Preclinical evidence also suggests that KDs act synergistically with radiotherapy, chemotherapy, and other therapies causing the production of reactive oxygen species such as hyperbaric oxygen [10, 11]. One mechanism is that KDs have been shown to inhibit glycolysis and the pentose phosphate pathway, thereby depriving cancer cells of important anti-oxidative substrates such as lactate, pyruvate, and glutathione. Indeed, the studies by Iyikesici on NSCLC [40] and pancreatic cancer [41] patients in which a KD was combined with chemotherapy, hyperbaric oxygen, and hyperthermia have shown very good efficacy with prolonged OS and PFS compared to historical controls. While the exact contribution of KD to these promising outcomes remains unclear, its synergistic supportive role would be consistent with the preclinical evidence.

Also in line with synergistic effects of a KD are the data by Khodabakhshi et al. [42] which revealed an OS benefit for the KD group compared to the control group in women receiving neoadjuvant chemotherapy for locally advanced breast cancer (Fig. 2); however, no such benefit was observed for the subgroup of metastasized patients in which 3 of 5 patients on the KD had died (Fig. 3). While this result appears disappointing, the small number of patients in this subgroup requires cautious interpretation.

Small patient numbers have also been a problem in the clinical trials on high-grade glioma patients thus far. In these patients, a KD consumed during salvage therapy with bevacizumab [33] or during standard radiochemotherapy with temozolomide [34] resulted in similar or slightly longer OS outcomes compared to patients on a standard diet receiving the same anti-tumor therapies. However, besides small patient numbers, a problem with these studies was that comparison with a control group was not planned a priori. Much preclinical research has concentrated on high-grade gliomas and other brain tumors and provided evidence for the efficacy of KDs combined with pro-oxidative therapies in these settings [69–72]; in addition, case reports have been published claiming therapeutic efficacy of KD in high-grade glioma patients [73–75]. A Bayesian meta-analysis pooling clinical and animal data together also concluded that combining a KD with other treatments was more likely to be effective than not against high-grade gliomas [7]. However, the clinical data summarized here must be rated as insufficient to highly confirm or provide evidence for such efficacy claims. Nevertheless, the evaluation of OS and PFS is a step in the right direction that future and larger studies should continue to follow.

Finally, it is important that the safety of a KD during cancer treatment has been further established by the analyzed studies. Except for the ketolung study [35] which observed a grade 4 hyperuricemia putatively related to KD, no major diet-related side effects have occurred. Again it is noteworthy that this study applied an extreme and partially artificial KD—it contained only 8% protein which must be considered inadequate for meeting the demands of cancer patients undergoing radiochemotherapy [76]. If diets are designed based on real foods containing high-quality protein and ample amounts of vegetables [77], there should be no basis for fundamentalist skepticism against KDs for cancer patients.

In summary, we conclude that the evidence base of KDs as supportive cancer therapies is growing and suggesting several beneficial effects. The largest evidence so far is for beneficial effects on body composition in both overweight and frail patient populations. Given the heterogeneity of studies and the novelty of the approach, we consider the glass of evidence for beneficial effects of KDs during cancer therapy as neither half full nor half empty. The hope is that future studies overcoming some of the weaknesses discussed here will continue to fill this glass.

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Compliance with ethical standards

Conflict of interest Rainer J. Klement, Nanina Brehm, and Reinhart A. Sweeney declare that they have no conflict of interest.

Ethical approval This review was undertaken without requesting ethical approval, since ethical approval was granted for most of the included studies. All human data were anonymous, and the ethical recommendations of the Declaration of Helsinki were adhered to.

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