A systematic review of the use of ketogenic diets in adult patients with cancer

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Abstract

Background

A growing body of evidence indicates the importance of nutrition in cancer treatment. Ketogenic diets are one of the strategies that have been proposed to enhance traditional anti-cancer therapy. This review summarises the evidence on the effect of oral ketogenic diets on anthropometry, metabolism, quality of life (QoL) and tumour effects whilst documenting adverse events and adherence in patients with cancer.

Methodology

We searched electronic databases using medical subject headings (MeSH) and text words related to ketogenic diets and cancer. Adult patients following a ketogenic diet as a complementary therapy prior, alongside or after standard anti-cancer treatment for longer than 7-days were included. Studies were assessed for quality using the Critical Appraisal Skills Programme tools.

Results

Eleven studies were included with 102 participants, (age range 34-87 years) from early phase trials, cohort studies and case reports. Studies included participants with brain, rectal or mixed cancer sites with early or advanced disease stage. The duration of intervention ranged from 2.4-134.7 weeks (0.5-31 months). Evidence was inconclusive for nutritional status and adverse events. Mixed results were observed for blood parameters, tumour effects and QoL. Adherence to diet was low (50 out of 102, 49%) and ranged from 23.5-100%.

Conclusion

High-quality evidence on the effect of ketogenic diets on anthropometry, metabolism, QoL and tumour effects is currently lacking in oncology patients. Heterogeneity between studies and low adherence to diet affects the current evidence. There is an obvious gap in the evidence highlighting a need for controlled trials to fully evaluate the intervention.

Introduction

There is a growing recognition of the impact of nutritional interventions on health outcomes [1; 2] and supportive health seeking behaviour of people with cancer [3; 4]. As part of this phenomena, ketogenic diets (KD) have generated interest due to their potential to affect cancer metabolism.

KD are high in fat and low in carbohydrate [5]. The exact proportions of macronutrients depend on specific type of diet [6; 7; 8; 9]. The most frequently used diet is a 4:1 fat to carbohydrate+protein ratio diet [6; 10]. The diet is based on complex physiological adaptations enabling increased utilisation of fat and ketones [5].

A justification for KD is based on Otto Warburg's observation that most cancer cells follow an altered metabolic pathway, relying on anaerobic glycolysis, even in the presence of oxygen [11]. Also, cancer cells strategically use glycolysis for rapid cell proliferation [12] and metastases formation [13]. Data from cellular and animal studies support and extend Warburg's conclusions [14; 15; 16; 17]. Reviews concentrating on tumour-suppressive mechanisms behind the diet combine available data from cellular, animal and clinical studies [15; 18; 19; 20]. Clinical evidence alone was reviewed in four articles. However, these reviews have a number of limitations including unspecified inclusion criteria, combining studies of parenteral and enteral nutrition, short duration on a KD that would not result in any potential benefits that could be attributed to ketosis, and studies that did not report or measure ketones [21; 22; 23; 24]. In addition, none of the studies assessed the quality of evidence using risk assessment tools. Currently, rigorously reviewed evidence from a dietetic perspective on oral KD is lacking.

KD have the potential to influence many physiological processes. Patients with cancer may incur weight loss, muscle wasting, and severe inflammation [25] which can lead to morbidity and poorer quality of life (QoL)[26]. It is therefore important to determine if KD adversely affect nutritional status in people with cancer.

The aim of this systematic review is to evaluate the current evidence on anthropometry, metabolic changes and systemic inflammation in people with cancer following a KD.

Materials and methods

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 15 September 2017 (registration number

CRD42017074011) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27].

Data sources, search strategy and selection criteria

We identified relevant studies using medical subject headings (MeSH) and text words related to KD and cancer. The following databases were searched: MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and PROSPERO. Conference abstracts were included in the search, along with ClinicalTrials.gov to identify ongoing trials. The main search strategy was created by a specialist librarian and was amended for the other databases (Supplementary Material A). Identified non-English language studies were translated.

Randomised and nonrandomised control trials, prospective cohort studies, retrospective cohort studies, observational and case studies with adults (>18 years) diagnosed with any type of cancer, at any stage of treatment receiving a KD were included. A KD was defined as any dietary manipulation of fat, carbohydrate and protein in order to achieve ketosis [5]. Studies that used KD as a complementary therapy prior, alongside or after standard anti-cancer treatment for longer than 7-days were included. We excluded studies that did not monitor ketosis during the intervention and studies with more than one intervention.

The primary outcome was changes in anthropometrics, namely body weight, the proportion of muscle mass and fat mass. Secondary outcomes were metabolic changes including glucose level, insulin level, insulin growth factor 1 (IGF-1), cholesterol and lipid levels, C- reactive protein (CRP), ketone levels, tumour size, tumour growth markers, QoL, adherence and adverse events.

The results of the literature searches were uploaded to Covidence (Version 1.0, Denmark, 2017). Duplicates were removed. The titles and abstracts were independently screened by two researchers, full text of selected abstracts were obtained and screened to identify the eligible publications; see PRISMA flow diagram [27].

Quality appraisal

Studies were assessed for quality using the Critical Appraisal Skills Programme tools for cohort studies (CASP) [28](Supplementary Material B).

Data synthesis

No studies were suitable for pooling the results, so a narrative analysis was presented.

Results

A total of 2367 titles were identified. In addition, 15 studies were found through manual searching. After removal of 130 duplicates, 2252 abstracts were screened, and 2217 studies then excluded. Subsequently, 35 full texts were assessed for eligibility. From those, 24 were excluded (details in Supplementary Material C). Eleven studies were included. See PRISMA diagram (Figure1).

Synthesis

Study characteristics

We included three early phase single arm clinical trials [29; 30; 31], three prospective cohort studies [32; 33; 34], one retrospective review [35] and four case reports [6; 36; 37; 38]. Only two studies were designed to compare intervention and control groups, one retrospective review [35] and one prospective study [34]. A total of 102 participants followed KD and the age ranged between 34 to 87 years. Mean baseline body mass index (BMI) ranged from 23.5±6 to 29.46±5 kg.m^2. Participants in eight studies had advanced cancer stage [31; 32; 33; 34; 35; 36; 38]. In three studies, cancer stage ranged from an early to more advanced stage [6; 29; 37]. Five studies involved participants with brain cancer [31; 34; 35; 36; 38], one study rectal cancer [6] and five studies had participants with mixed cancer sites [29; 30; 32; 33; 37]. Duration of intervention ranged from 2.4 to 134.7 weeks. KD were used as a sole therapy or in combination with standard therapies, and this differed not only between studies but within studies (Table 1).

Study quality

Quality of evidence was very low. The cohort studies had limited information on participants' eligibility and details of recruitment were only reported in two studies [30; 31]. Exposure to KD was only accurately measured in one study [33] which monitored ketosis, energy and nutrient intake. Outcomes were accurately measured in three studies [29; 32; 33]. All studies identified the main confounding factors; however, no study adjusted for them. Follow up was long enough in all studies. Studies lacked precision and reliability, having

small sample size, insufficient statistical analysis, and multiple limitations in the design, methodology and outcomes reported.

Intervention

All studies investigated the effect of oral KD; however, there was considerable variation in how the diet was delivered. Three studies followed a traditional KD with 4:1 or 3:1 fat to carbohydrate+protein ratio (F:CHO+P) [29; 34; 38], two studies used ratio F:CHO+P between 0.7:1 to 1.8:1 [33; 37], three studies used Modified Atkins diet (20-40g/day CHO) [30; 35; 36], two studies used low glycaemic index diet (< 70g/day CHO) [31; 32] and one study used Paleolithic KD with F:P ratio 2:1[6].

All studies encouraged participants to eat to satiety, however, only two studies reported on energy and macronutrient intake [33; 37]. Four studies involved a dietitian or nutritionist [29; 34; 37; 38], and seven studies applied some form of dietary monitoring which included a tailored dietary regimen with provided meals [29], food diaries [37], dietary recall [33], diet software [35], telephone calls [38], or telephone calls and in-person visits [6; 32]. The adherence was assessed by study completion and measuring the level of ketosis. Urine ketosis was measured with or without blood analysis taken daily, weekly, biweekly or at set time points (Supplementary Material D).

Primary and secondary outcomes

Anthropometry

Nine studies measured body weight and reported a mean weight loss of 1.86 kg to 13 kg. Weight was measured between 2.4 weeks to 97.8 weeks (22.5 months). Fine (2012) monitored energy intake, observing a 4% mean decrease in weight but a mean energy deficit of 35% [33]. Klement (2016) also monitored energy intake and observed significant weight loss albeit in patients on a hypocaloric diet intending to lose weight [37]. Champ (2014) reported similar findings [35]. Five studies [6; 29; 30; 31; 32; 36] reported a significant reduction in weight, but did not report on energy intake. One study did not observe a significant weight loss [36]. Five studies reported a decrease in BMI [6; 30; 32; 36; 38] consistent with weight loss. Body composition was measured by one study [37]; observing a decrease in fat mass and an increase in muscle mass relative to body weight (Table 2).

Biochemical parameters

Blood glucose

Ten studies assessed blood glucose at baseline and follow up. Four studies reported a decrease in blood glucose [6; 32; 33; 35], five reported no significant changes [29; 30; 31; 36; 37] and one study showed problems with maintenance of glucose below 80 mg/dl [38]. Two studies reported on correlation between beta hydroxyl butyrate (BHB) and glucose concentration. One study found significant negative correlation (p=0.05) [37], while other reported no significant change [30].

Lipid profile

Seven studies reported on changes in blood lipids. Four studies did not observe any significant changes in triglycerides (TG), cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) [30; 31; 36; 37]. One study reported a significant drop in LDL and HDL [32]. One study observed elevated lipid enzymes, with stable TG [6] and two studies reported an elevated cholesterol and LDL [6; 38].

Other parameters

Studies reported on kidney [6; 30; 33], liver [6; 30; 32; 37] and thyroid function [6; 37] with no changes in measured markers. Also, there were no differences in inflammatory markers in two studies [33; 37], while one study reported a decrease in CRP [6]. A negative correlation between BHB and insulin but not IGF-1 and IGF-2 were reported in one study [33]. The decrease in insulin was observed in participants who achieved a 10 to 35 fold increase (p=0.018) in ketosis [33], however, no changes were reported in another study [37]. In participants with diabetes, one reported a 75% decrease in insulin taken compared to baseline [32] and one stopped insulin doses completely [30]. One study reported a significant increase ($p<0.05$) in the level of the plasma protein carbonyl (biomarker of oxidative stress) compared to baseline [29]. For details on all biochemical parameters see Table 2.

Tumour effects

All eleven studies reported on tumour stability and progression, however, the diagnostic tool used was only reported in eight studies; four used magnetic resonance imaging [6; 31; 34; 38], three used positron emission tomography [30; 33; 38], and one used computed tomography scans [30]. Due to low compliance, most of the studies could not perform any probability statistical analysis on effect size. One study compared results between

participants who were adherent or not adherent to the diet [33]. Patients with 3-fold higher ketosis had stable disease or partial remission compared to those with progressive diseases (p=0.018) [33]. One study reported 50% reduction in seizure frequency after 13.2 months follow up [36]. Some studies reported outstanding results in some patients, whilst in others the disease progressed (Table 2).

Survival

Zahra (2017) showed no difference in survival between patients who adhered to a diet and those who stopped after 22 months [29]. Champ (2014) reported that four patients were alive, three with recurrence after 14 months of follow up, one patient without recurrence for 12 months and two patients died after 6.3 months and 20 months [35]. Rieger (2014) showed that patient's survival from the time of the diet was 32 weeks (range 6 to 86 weeks) and compared survival with patients treated with standard therapy, however, results showed no difference. Further, the study showed a trend in longer progression free survival in patients with stable ketosis (p=0.069) [31]. In the study by Tan-Shalaby (2016), from the four patients that completed the intervention, survival ranged from 40 to 131 months from the start of the diet [30]. In the study of Klement (2016), five patients with an early cancer were alive at 4 months follow up and one patient with metastatic cancer died 11 months from diagnosis [37]. Only one study compared reported and expected survival [36] indicating survival of 13 months versus expected 7.8 months in one patients and 17 months compared to expected 7.4 months in another.

Adherence

From 102 patients who started a KD intervention, 50 (49%) were able to complete the diet.

Ketosis

All studies reported ketosis; however not all patients were able to maintain ketosis. Ketosis was relatively low and ranged between 0.03 to 15 mmol/L (Table 2). Only Tan-Shalaby (2016) investigated whether patients achieved the glucose ketone index [30] that has been proposed to monitor the efficacy of metabolic therapy [39], however, patients did not achieved values predicted for therapeutic effects (<1.0)(Supplementary Document D).

Adverse events

In total, adverse events were reported in 50 patients. Eight studies measured adverse events [29; 30; 31; 32; 33; 35; 37; 38] and four used a validated tool [29; 33; 35; 37]. Most studies reported fatigue, constipation, diarrhoea, hyperuricemia and vomiting. From 50 patients,

16 reported fatigue, 12 constipation, 8 diarrhoea, 8 hyperuricemia and 4 vomiting. One study reported hunger in 2 and craving for sugar in 5 out of 12 patients [31]. Hyperkalaemia and hypokalaemia were reported in 2 patients. Also, 2 patients experienced leukocytopenia. Adverse events such as oesophagitis, anaemia, hypomagnesemia, pedal oedema, halitosis, hypoglycaemia, hyperlipidaemia and deep vein thrombosis were observed only once across studies.

Quality of life

Three studies assessed the QoL with validated European Organization for Research and Treatment core quality of life questionnaire [30; 32; 37]. No consistent results were reported.

Discussion

From hypothetical conjecture based on academic modelling supported by animal and cellular studies, KD have a sound theoretical bases for suppressing tumour growth [11; 20; 21]. However, strong conclusive evidence in clinical practice is still lacking.

Current studies demonstrated that patients on KD lose weight. This is of concern for sarcopenic and malnourished patients as body composition and nutritional status have been shown to influence clinical outcomes [25; 40]. However, most of the studies did not monitor energy intake, and it is very likely patients followed a hypocaloric diet. This was demonstrated in two studies [32; 37] and possibly attributed to self-administrated diet and limited diet monitoring. Also, it is widely accepted that body weight is a weak predictor of changes in health status [41], as patients might lose fat but not muscle mass [37]. Hence, further studies of KD that control energy and macronutrient intake and measure body composition are required.

This review found a low adherence to KD possibly due to a number of factors. The proportion of macronutrients influence ketosis. Studies followed variable F:CHO+P ratio, and thus the ketosis may have been affected by levels of carbohydrate and protein. It was originally proposed that carbohydrate should be maintained below 20g per day but no data exist to define what level of carbohydrate represents a threshold for maintenance of ketosis [20]. Studies in this review used a great variation of carbohydrate, reaching to 70g per day. Also, it has been suggested that a very high protein intake may counteract the level of ketosis by providing glucogenic amino acids for production of glucose when the

level of protein exceeds the normal non-starvation protein turnover [20]. Hence, the carbohydrate and protein ratio may explain a low ketosis.

Furthermore, the maintenance of ketosis and adherence to KD are very likely underpinned by limitations in the delivery of the diet and monitoring. Schwartz (2015) suggested that patients require weekly contact with a dietitian [38]. However, most of the studies tested self-administrated diet and had little control over the food selection, energy and nutritional composition. In contrast, Zahra (2017) provided tailored meals but the compliance was still poor, indicating that delivery of the diet represents only one contributor to adherence. The author concluded that patients found a 4:1 fat to carbohydrate ratio unpalatable [29].

Possibly, palatability plays a crucial role and patients are unlikely to follow a restricted diet for a prolonged period of time. There were no obvious differences in adherence between studies with the original 4:1 KD and those using a Modified Atkins diet or similar macronutrient ratio. The evidence indicates that following the diet is difficult for patients, especially incorporating the diet into family life [32]. Schmidt (2011) suggested that patient's motivation is critical [32] and that diet would only be a good option in highly motivated patients.

Furthermore, the adherence is closely related to adverse events. It is difficult to differentiate between events related to treatment and those specific to the diet, especially in very advanced cancer. Constipation, diarrhoea and fatigue were the most frequently reported problems. Due to low dietary fibre content, patients following a KD are likely to experience constipation. Studies that reported on dietary fibre showed a range between 7.9 g - 12.5 g/day, while 20-30 g/day is recommended [42]. On the other hand, if a substantial proportion of fat in a diet, is not introduced gradually, it might lead to diarrhoea [43]. Also, a decrease in carbohydrate intake and simulation of fasting may lead to fatigue. These adverse events were more frequent in the first four weeks on a diet, indicating that time for adaptation is required [32].

Concerns about acidosis, kidney and hepatic functional impairment have not been confirmed. Two studies reported hyperuricemia, which needs further investigation. Many adverse events were reported as single cases, indicating the importance of considering comorbidities when prescribing the diet [35].

Mixed results were observed in blood parameters, tumour, quality of life and survival. No clear trend in changes of glucose and lipids could be concluded. Inverse correlation between glucose and ketones level was demonstrated only in two studies [33; 37]. Tumour

responses were better in patients with early stage of disease [32; 37] or with low-grade tumours when the ketogenic diet was used as a sole therapy [34]. Patients with stable disease or partial remission were able to achieve 3-fold higher ketosis than patients with more progressive disease [33]. Some patients achieved outstanding results on tumour stability and survival while others progressed. Most of the studies included mixed cancer populations, and thus its is unclear what cancer site could benefit from the diet the most. However, positive responses where clearly observed in patients with brain tumours. The quality of life parameters slightly improved, worsened or remained unchanged . However, due to high level of bias, a small number of patients who had a high level of adherence to the diet, and no control group, conclusions are difficult to ascertain from the available data.

Conclusion

Current studies represent preliminary evidence and show that the KD is potentially feasible and does not cause life-threatening events in patients with cancer. However, adherence is low and possibly linked to a limitation in diet delivery, the lack of monitoring and follow up. A high level of heterogeneity among studies prevents the formulation of conclusions. To develop the evidence base for the use of KD in clinical practice, high quality control trials are required.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest. No funding has been received. Non-financial support has been provided by the University of Manchester.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with PROSPERO) have been explained. The reporting of this work is compliant with PRISMA guidelines.

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram

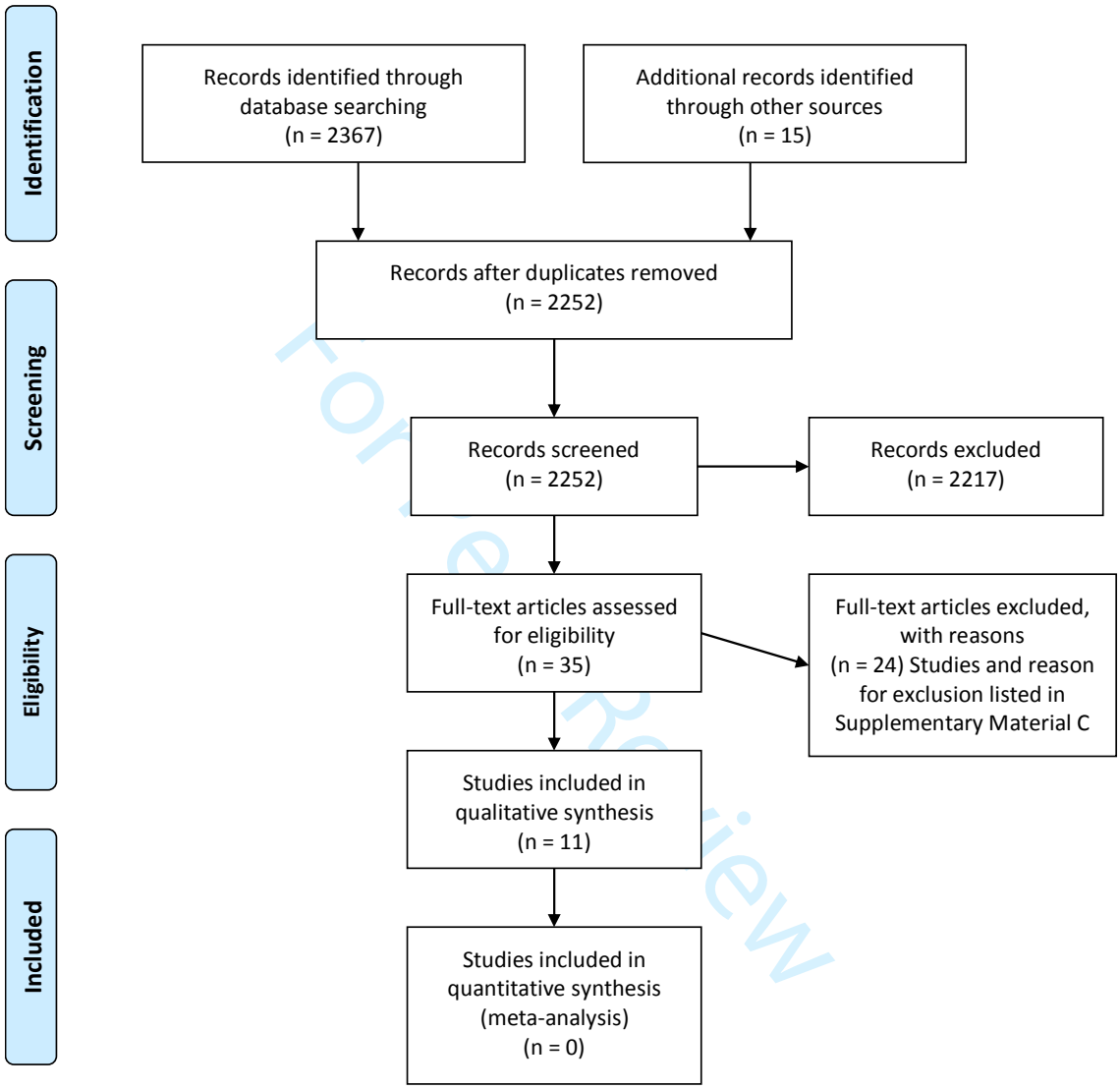

Table 1 Studies characteristics

Author/ Year	Design	Sample	Median Age	Cancer Site (n)	Cancer Stage	Treatment Received (n)	Intervention	Duration weeks	Outcomes
Zahra 2017	Single arm pilot trial	9	60 (55-83)	Lung (7) Pancreatic (2)	2 to 4	Chemotherapy, radiation	T, KD	5.5-7	AE, ketone, glucose levels, oxidative stress, PFS
Rieger 2014	Single arm pilot trial	20	57 (32-72)	Recurrent glioblastoma	Advanced	Radiotherapy, chemotherapy	SA, KD	6-16	Adherence, PFS, survival, QoL seizures frequency, ketosis,
Tan-Shalaby 2016	Single arm feasibility trial	17	64 (42-87)	Mixed	Advanced	No therapy (4)/ chemotherapy	SA, Modified Atkins diet	4-16	Safety, tolerability adverse events, BC, blood pressure, BP
Fine 2012	Single arm feasibility trail	12	Mean/SEM 62.9 ±2.5	Mixed	Advanced	Chemotherapy PI	SA, KD	4	Adherence, AE, metabolic effects
Artzi 2017	Prospective cohort study	9 (5 KD)	42 (37-69)/ 46 (27-64)	Mixed	Advanced	No therapy/ chemotherapy	T, KD	2-31 months	brain metabolites, tolerability, tumour effect
Schmidt 2011	Prospective single arm pilot study	16	50.5 (30-65)	Mixed	Advanced	Chemotherapy/ radiation/ immunotherapy	SA, KD	12	QoL, BC, BP, tumour effect
Champ 2014	Retrospective study	53 (6 KD)	59.5 (34-62)	Glioblastoma multiforme	Stage 3 to 4	Chemotherapy/ chemo-radiation	SA, KD	3-12 months	Safety, toxicity, survival, glucose level
Strowd 2015	Case reports	8	Mean/SD 41.5 ±10	Mixed	Advanced	No therapy/ chemotherapy	SA, Modified Atkins diet	2-24 months	Adherence, BC, tumour effect
Klement 2016	Case reports	6	62 (40-74)	Mixed	Stage 1 to 4	Radiation/radio-chemotherapy	SA, KD	32-73+ days	QoL, BC, BP
Schwartz 2015	Case reports	2	55 and 52	Glioblastoma multiforme	Advanced	Surgery/radiation/ chemotherapy PI	SA, KD	12	Adherence, BP, tumour effect
Toth 2016	Case report	1	62	Rectal	Early stage	Radiation PI	SA, KD	22.5 months	Adherence, AE, IP, organs function, BP, tumour effect

AE - adverse events, BC- body composition, BP- biochemical parameters, IP- intestinal permeability, Interv -intervention, KD- ketogenic diet, SA- self administrated, PFS- progression free survival, QoL- quality of life, PI- prior intervention, SD- standard deviation, SEM- standard error of the mean, T-tailored, vs- versus

Table 2 Outcomes reported in the included studies

Study	Mean body weight change	Body composition	Blood glucose	Lipid profile	Other blood measures	Tumour effects	Adherence
Zahra 2017	lung pts -5.6 kg pancreatic pts -8.15 kg	NR	NSD	NR	↑ protein carbonyl vs baseline	2 stable, 7 progressed	3/9
Rieger 2014	-1.86 kg	NR	NSD	NSD in TG, cholesterol, HDL, LDL	NSD in HbA1c values	1 complete, 5 partial responses, 1 NR	8/20
Tan-Shalaby 2016	-12.3 ± 6.0 kg	NR	NSD	NSD in cholesterol LDL, HDL, TG	NSD in urea nitrogen/creatinine ratio, creatinine, albumin and uric acid	3 stable,1 reduced symptoms	4/17
Fine 2012	-3kg SME 0.5	NR	mean/SEM ↓ 3.2 (±3.7) mg/dl vs baseline	NR	↓ in insulin by 75% to 90% vs baseline	5 stable, 1 partial remission, 4 progressed	5/12
Artzi 2017	NR	NR	NR	NR	NSD in brain metabolism	1 stable, 4 progressed	4/5
Schmidt 2011	-2kg	NR	with exception of 1 pt all ↓	↓ in pts with elevated TG, cholesterol, sig ↓ mean LDL, HDL	sig improved liver parameters, 1pt with diabetes ↓ 75% of initial insulin units	5 progressed, 5 stable	5/16
Champ 2014	-7.9 kg	NR	↓ from mean 142.5 (82-181) mg/dl to 84 (76-93) mg/dl	NR	NR	5 progressed, 1 without recurrence for 12 months	6/6

Strowd 2015	-3.4±6.5 kg	NR	NSD	NSD in cholesterol, LDL, HDL, TG	NSD in creatinine	5 (63%) at least 50% reduction in seizure frequency, 4 seizures free	7/8
Klement 2016	↓ NR	sig FM ↓ FFM ↑ relative to body weight	NSD	NSD in LDL, HDL, cholesterol, TG	NSD in CRP, IGF-1, TSH, creatinine, HbA1c, insulin, ALT, AST	5 tumour regressions, 1 progressed	6/6
Schwartz 2015	NR	NR	1 after discharge ↑ > 80 mg/dl, 1 not below 80 mg/dl	1 cholesterol ↑ to 281 at 6 weeks, after 12 weeks to 252, LDL ↑ to 197 after 6 weeks, to 182 at 12 weeks	NR	progressed	1/2
Toth 2016	-13 kg	NR	decrease	↑ lipid enzymes, slight ↑ cholesterol, LDL, TG low	normal renal, liver, thyroid, inflammatory markers	↓ tumour markers, stable on diet, after 24 months progressed	1/1

ALT- alanine aminotransferase, AST- aspartate aminotransferase, BHB -beta hydroxy butyrate, CRP - C reactive protein, FM - fat mass, FFM - fat free mass, HDL- high density lipoprotein, HbA1- haemoglobin A1, IGF 1/2 - insulin-like growth factor1/2, LDL -low density lipoprotein, NR-not reported, NSD -no significant difference, pt/pts-patient/s sig- significant, TG -triglycerides, vs -versus

Supplementary Document A – Search strategy

MEDLINE search – Ovid interference

1. ketogenic diet.mp. or Ketogenic Diet/

2. carbohydrate restricted diet.mp. or Diet, Carbohydrate-Restricted/

3. high fat diet.mp. or Diet, High-Fat/

4. cancer.mp. or Neoplasms/

5. (tumor or tumour or carcinoma or sarcoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. 1 or 2 or 3

7. 4 or 5

8. 6 and 7

9. limit 8 to humans

10. limit 9 to "all adult (18 plus years)"

Authors note

While creating the search strategy, we considered including body composition, metabolism, inflammation, chemotherapy, radiotherapy as key words, however, the search results were unnecessary reduced. With the proposed general search, we judged that there was a higher chance to reach all the relevant publications.

Supplementary Document B - Quality Assessment using the Critical Appraisal Skills Programme tools for cohort studies

Author/ Year	Design	Clearly addressed issue?	Cohort recruitment acceptable?	Exposure accurately measured to minimise bias?	Outcomes accurately reported to minimise bias?	All important confounding factors identified?	Confounding factors taken into account in analysis?	Following up of subjects complete enough?	Following up of subjects long enough?	What are the results?	How precise are the results?	Are results reliable?	Can results be applied to the local population ?	Fit results with other available evidence?	What are the implications for practice?
Zahra 2017	Single arm pilot trial	Yes	No	No	Yes	Cannot tell	No	Yes	Yes	Adherence, survival	95% CI not given	Cannot tell	No	Yes	NIL
Rieger 2014	Single arm pilot trial	Yes	No	No	No	Yes	No	Yes	Yes	Feasibility, survival	95% CI not given	Cannot tell	Yes	Yes	NIL
Tan-Shalaby 2016	Single arm feasibility trial	Yes	Yes	No	No	Yes	No	Yes	Yes	Feasibility, QoL, survival	95% CI not given	Cannot tell	No	Yes	NIL
Fine 2012	Single arm feasibility trial	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Feasibility, safety, tumour effects	Yes but not all outcome s	Cannot tell	No	Yes	NIL
Artzi 2017	Prospecti ve cohort study	Yes	No	No	No	Yes	No	Yes	Yes	Brain metabolism changes	CI 95% not given	Cannot tell	Yes	Yes	NIL
Schmidt 2011	Prospecti ve single arm pilot study	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Tolerability, QoL, biochemical markers	CI 95% not given	Cannot tell	No	Yes	NIL

Supplementary Document C Excluded studies

Study/ Year	Reason for exclusion based on our study selection criteria
Abdelbary 2017 [44]	abstract (conference published)
Anderson 2016 [45]	abstract (conference published)
Bozzetti 1996 [46]	parenteral nutrition
Bozzetti 2004 [47]	parenteral nutrition
Branca 2015 [48]	two interventions = ketogenic diet and vitamin D intervention
Breitkreutz 2005 [49]	ketones not measured
Brünings 1941 [51]	two interventions = ketogenic diet and insulin intervention
Brünings 1942 [50]	two interventions = ketogenic diet and insulin intervention
Chaiyasit 217 [52]	abstract
Chu-Shore 2010 [53]	study with children
Cohen 2016 [54]	abstract (conference paper)
Fearon 1988 [55]	short intervention
Jansen 2016 [56]	ketones not measured
Moore 2012 [57]	overview from clinical practice
Nebeling 1995 [8]	study with adolescent girls
Renda 2015 [58]	abstract
Rossi-Fanelli 1991 [66]	parenteral nutrition
Santos 2017 [59]	two interventions = ketogenic diet and perillyl alcohol intervention
Shinojima 2017 [60]	study with children
Schmidt 2008 [61]	abstract
Schroeder 2013 [62]	short intervention
Schwalb 2016 [63]	abstract
Shulte 1942 [64]	two interventions = ketogenic diet and insulin intervention
Zuccoli 2010 [66]	two interventions = ketogenic diet and fasting

Supplementary Document D – Diet delivery

Author Year	Nutrition details	Delivery of diet	Ketosis monitoring	Mean baseline nutritional status	Diet monitoring	Dietitian involved	Intervention duration [weeks]	Actual length on diet [weeks]
Zahra 2017	F:CHO+P ratio 4:1, F 90%, P 8%, CHO 2%	Commercial powder drink, modified meals, discretionary food	Weekly in serum, daily-finger stick, (0.6-6 mmol/l)	NR	Metabolic kitchen meals	Yes	5.5 to 7	Mean lung pts 2.4, pancreatic pts 3
Rieger 2014	CHO max 60 g/day	Fermented yoghurt drinks, two plant oils.	2-3 times a week, (0.03 - 1 mmol/l)	78.3±16.1 kg	NR	NR	6-16	Median 5 weeks (range 3-16)
Tan-Shalaby 2016	CHO 20-40 g/day	Meat, fish, dairy, green leafy vegetable	Baseline, 4, 6, 8 weeks. (at 4 weeks mean 12.08 mg/dl, at 8 weeks 6.17 mg/dl)	92±2.3 kg, 29.46±5 kg/m^2	NR	NR	16	4 to 16
Fine 2012	EI 1236 kcal, CHO 27 g/day, F 81 g/day, P 89.5 g/day	Increased fat and protein consumption	Weekly in serum, (mean/SEM 10.9 ± 1.7 mg/dl)	Mean/SEM 73±0.9kg 27.2±1.2kg/m^2	Dietary recall	NR	4	26 to 28 days
Artzi 2017	F:CHO+P ratio 4:1	Commercial drink and soya bean diet	Daily in urine, (score 2+ to 4+, high)	NR	NR	Yes	NS	2 to 31 months
Schmidt 2011	CHO <70 g/day	Two oil-protein shakes, 1 tablespoon of the oil with 3 main meals	Daily in urine, (1 to 8 mmol/l)	68.5±6.8 kg 23.5±6.0 kg/m^2	In person, phone calls	NR	12	12

Champ 2014	CHO 30-50 g/day 8%, F 77%, P 15%,	Vegetable, meat, fish, egg, cream, nuts and oils	Biweekly in serum, daily in urine (NR/5.6/14.1 mg/dl)	85.7kg	Diet software	NR	NS	3 to 12 months
Strowd 2015	CHO 20g/day	High-fat foods. multivitamin, vitamin D, calcium	Biweekly then weekly, NR	78.8 ±18.3 kg 25.7±3.5kg/m^2	NR	NR	NR	Median 13.2 months (range 2-24)
Klement 2016	F:CHO+P ratio 0.8:1 to1.8:1, mean EI 2043.5 kcal, CHO 32.3g/day, P 100.2g/day, F 166.7g/ day	Olive, coconut oil, butter, ghee, fatty fish, cheese, meat and non-starchy vegetables	Daily in urine, 3x in blood, (0.03 to 1.31 mmol/l)	82.02 kg	Food diaries	Yes	NS	32 to 73+ days
Schwartz 2015	F:CHO+P ratio 3:1, P 0.6 g /kg body weight	Commercial drink	Daily in blood, (score 2 to 4)	27 kg/m^2 24.3 kg/m^2	Phone calls	Yes	12	4 to 12
Toth 2016	F- P ratio 2:1	Meat and fat, root vegetables < 30%	Daily in urine, (score 1+ to 3+)	78 kg 25.5 kg/m^2	Personal visits, phone calls, emails	NR	NS	22.5 months

CHO- carbohydrate, F- fat, NR- not reported, NS - not stated, P-protein, pt/pts- patient/s