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

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1 **Abstract**

2 **Background**

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

8 **Methodology**

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

14 **Results**

15 Eleven studies were included with 102 participants, (age range 34-87 years) from early
16 phase trials, cohort studies and case reports. Studies included participants with brain,
17 rectal or mixed cancer sites with early or advanced disease stage. The duration of
18 intervention ranged from 2.4-134.7 weeks (0.5-31 months). Evidence was inconclusive for
19 nutritional status and adverse events. Mixed results were observed for blood parameters,
20 tumour effects and QoL. Adherence to diet was low (50 out of 102, 49%) and ranged from
21 23.5-100%.

22 **Conclusion**

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

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31 Introduction

32 There is a growing recognition of the impact of nutritional interventions on health outcomes
33 (1; 2) and supportive health seeking behaviour of people with cancer (3; 4). As part of this
34 phenomena, ketogenic diets (KD) have generated interest due to their potential to affect
35 cancer metabolism.

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

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

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

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

59 Materials and methods

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

1
2 62 CRD42017074011) and followed the Preferred Reporting Items for Systematic Reviews
3 63 and Meta-Analyses (PRISMA) guidelines ⁽²⁷⁾.
4
5 64

6 65 Data sources, search strategy and selection criteria

7
8
9 66 We identified relevant studies using medical subject headings (MeSH) and text words
10 67 related to KD and cancer. The following databases were searched: MEDLINE, Embase,
11 68 CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and
12 69 PROSPERO. Conference abstracts were included in the search, along with
13
14 70 ClinicalTrials.gov to identify ongoing trials. The main search strategy was created by a
15 71 specialist librarian and was amended for the other databases (Supplementary Material A).
16
17 72 Identified non-English language studies were translated.
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21 73 Randomised and nonrandomised control trials, prospective cohort studies, retrospective
22 74 cohort studies, observational and case studies with adults (>18 years) diagnosed with any
23 75 type of cancer, at any stage of treatment receiving a KD were included. A KD was defined
24 76 as any dietary manipulation of fat, carbohydrate and protein in order to achieve ketosis ⁽⁵⁾.
25
26 77 Studies that used KD as a complementary therapy prior, alongside or after standard anti-
27 78 cancer treatment for longer than 7-days were included. We excluded studies that did not
28 79 monitor ketosis during the intervention and studies with more than one intervention.
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33
34 81 The primary outcome was changes in anthropometrics, namely body weight, the
35 82 proportion of muscle mass and fat mass. Secondary outcomes were metabolic changes
36 83 including glucose level, insulin level, insulin growth factor 1 (IGF-1), cholesterol and lipid
37 84 levels, C- reactive protein (CRP), ketone levels, tumour size, tumour growth markers, QoL,
38 85 adherence and adverse events.
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42 86 The results of the literature searches were uploaded to Covidence (Version 1.0, Denmark,
43 87 2017). Duplicates were removed. The titles and abstracts were independently screened by
44 88 two researchers, full text of selected abstracts were obtained and screened to identify the
45 89 eligible publications; see PRISMA flow diagram ⁽²⁷⁾.
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49 90 Quality appraisal

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52 91 Studies were assessed for quality using the Critical Appraisal Skills Programme tools for
53 92 cohort studies (CASP) ⁽²⁸⁾(Supplementary Material B).
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56 93 Data synthesis

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

95

96 **Results**

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

102

103 *Synthesis*

104

105 Study characteristics

106 We included three early phase single arm clinical trials ^(29; 30; 31), three prospective cohort
107 studies ^(32; 33; 34), one retrospective review ⁽³⁵⁾ and four case reports ^(6; 36; 37; 38). Only two
108 studies were designed to compare intervention and control groups, one retrospective
109 review ⁽³⁵⁾ and one prospective study ⁽³⁴⁾. A total of 102 participants followed KD and the
110 age ranged between 34 to 87 years. Mean baseline body mass index (BMI) ranged from
111 23.5±6 to 29.46±5 kg.m². Participants in eight studies had advanced cancer stage ^{(31; 32; 33;}
112 ^{34; 35; 36; 38)}. In three studies, cancer stage ranged from an early to more advanced stage ^{(6;}
113 ^{29; 37)}. Five studies involved participants with brain cancer ^(31; 34; 35; 36; 38), one study rectal
114 cancer ⁽⁶⁾ and five studies had participants with mixed cancer sites ^(29; 30; 32; 33; 37). Duration
115 of intervention ranged from 2.4 to 134.7 weeks. KD were used as a sole therapy or in
116 combination with standard therapies, and this differed not only between studies but within
117 studies (Table 1).

118 Study quality

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

1
2 125 small sample size, insufficient statistical analysis, and multiple limitations in the design,
3 126 methodology and outcomes reported.

4
5 127 Intervention

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8 128 All studies investigated the effect of oral KD; however, there was considerable variation in
9 129 how the diet was delivered. Three studies followed a traditional KD with 4:1 or 3:1 fat to
10 130 carbohydrate+protein ratio (F:CHO+P)^(29; 34; 38), two studies used ratio F:CHO+P between
11 131 0.7:1 to 1.8:1^(33; 37), three studies used Modified Atkins diet (20-40g/day CHO)^(30; 35; 36),
12 132 two studies used low glycaemic index diet (< 70g/day CHO)^(31; 32) and one study used
13 133 Paleolithic KD with F:P ratio 2:1⁽⁶⁾.

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18 134 All studies encouraged participants to eat to satiety, however, only two studies reported on
19 135 energy and macronutrient intake^(33; 37). Four studies involved a dietitian or nutritionist^{(29;}
20 136 ^{34; 37; 38)}, and seven studies applied some form of dietary monitoring which included a
21 137 tailored dietary regimen with provided meals⁽²⁹⁾, food diaries⁽³⁷⁾, dietary recall⁽³³⁾, diet
22 138 software⁽³⁵⁾, telephone calls⁽³⁸⁾, or telephone calls and in-person visits^(6; 32). The
23 139 adherence was assessed by study completion and measuring the level of ketosis. Urine
24 140 ketosis was measured with or without blood analysis taken daily, weekly, biweekly or at
25 141 set time points (Supplementary Material D).

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31 143 *Primary and secondary outcomes*

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34 144 Anthropometry

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38 145 Nine studies measured body weight and reported a mean weight loss of 1.86 kg to 13 kg.
39 146 Weight was measured between 2.4 weeks to 97.8 weeks (22.5 months). Fine (2012)
40 147 monitored energy intake, observing a 4% mean decrease in weight but a mean energy
41 148 deficit of 35%⁽³³⁾. Klement (2016) also monitored energy intake and observed significant
42 149 weight loss albeit in patients on a hypocaloric diet intending to lose weight⁽³⁷⁾. Champ
43 150 (2014) reported similar findings⁽³⁵⁾. Five studies^(6; 29; 30; 31; 32; 36) reported a significant
44 151 reduction in weight, but did not report on energy intake. One study did not observe a
45 152 significant weight loss⁽³⁶⁾. Five studies reported a decrease in BMI^(6; 30; 32; 36; 38) consistent
46 153 with weight loss. Body composition was measured by one study⁽³⁷⁾; observing a decrease
47 154 in fat mass and an increase in muscle mass relative to body weight (Table 2).

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1 156 Biochemical parameters

2 157 *Blood glucose*

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6 158 Ten studies assessed blood glucose at baseline and follow up. Four studies reported a
7
8 159 decrease in blood glucose ^(6; 32; 33; 35), five reported no significant changes ^(29; 30; 31; 36; 37)
9
10 160 and one study showed problems with maintenance of glucose below 80 mg/dl ⁽³⁸⁾. **Two**
11 161 **studies reported on correlation between beta hydroxyl butyrate (BHB) and glucose**
12 162 **concentration. One study found significant negative correlation (p=0.05) ⁽³⁷⁾, while other**
13
14 163 **reported no significant change ⁽³⁰⁾.**

15
16 164 *Lipid profile*

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19 165 Seven studies reported on changes in blood lipids. Four studies did not observe any
20
21 166 significant changes in triglycerides (TG), cholesterol, high density lipoprotein (HDL) and
22 167 low density lipoprotein (LDL) ^(30; 31; 36; 37). One study reported a significant drop in LDL and
23
24 168 HDL ⁽³²⁾. One study observed elevated lipid enzymes, with stable TG ⁽⁶⁾ and two studies
25 169 reported an elevated cholesterol and LDL ^(6; 38).

26
27 170 *Other parameters*

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29
30 171 Studies reported on kidney ^(6; 30; 33), liver ^(6; 30; 32; 37) and thyroid function ^(6; 37) with no
31 172 changes in measured markers. Also, there were no differences in inflammatory markers in
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33 173 two studies ^(33; 37), while one study reported a decrease in CRP ⁽⁶⁾. A negative correlation
34
35 174 between BHB and insulin but not IGF-1 and IGF-2 were reported in one study ⁽³³⁾. The
36 175 decrease in insulin was observed in participants who achieved a 10 to 35 fold increase
37
38 176 (p=0.018) in ketosis ⁽³³⁾, however, no changes were reported in another study ⁽³⁷⁾. In
39
40 177 participants with diabetes, one reported a 75% decrease in insulin taken compared to
41 178 baseline ⁽³²⁾ and one stopped insulin doses completely ⁽³⁰⁾. **One study reported a**
42 179 **significant increase (p<0.05) in the level of the plasma protein carbonyl (biomarker of**
43
44 180 **oxidative stress) compared to baseline ⁽²⁹⁾.** For details on all biochemical parameters see
45
46 181 Table 2.

47
48 182 *Tumour effects*

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51 183 All eleven studies reported on tumour stability and progression, however, the diagnostic
52 184 tool used was only reported in eight studies; four used magnetic resonance imaging ^{(6; 31;}
53 185 ^{34; 38)}, three used positron emission tomography ^(30; 33; 38), and one used computed
54
55 186 tomography scans ⁽³⁰⁾. **Due to low compliance, most of the studies could not perform any**
56
57 187 **probability statistical analysis on effect size. One study compared results between**

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

193 Survival

194 Zahra (2017) showed no difference in survival between patients who adhered to a diet and
195 those who stopped after 22 months⁽²⁹⁾. Champ (2014) reported that four patients were
196 alive, three with recurrence after 14 months of follow up, one patient without recurrence for
197 12 months and two patients died after 6.3 months and 20 months⁽³⁵⁾. Rieger (2014)
198 showed that patient's survival from the time of the diet was 32 weeks (range 6 to 86
199 weeks) and compared survival with patients treated with standard therapy, however,
200 results showed no difference. Further, the study showed a trend in longer progression free
201 survival in patients with stable ketosis ($p=0.069$)⁽³¹⁾. In the study by Tan-Shalaby (2016),
202 from the four patients that completed the intervention, survival ranged from 40 to 131
203 months from the start of the diet⁽³⁰⁾. In the study of Klement (2016), five patients with an
204 early cancer were alive at 4 months follow up and one patient with metastatic cancer died
205 11 months from diagnosis⁽³⁷⁾. Only one study compared reported and expected survival
206⁽³⁶⁾ indicating survival of 13 months versus expected 7.8 months in one patients and 17
207 months compared to expected 7.4 months in another.

208 Adherence

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

210 Ketosis

211 All studies reported ketosis; however not all patients were able to maintain ketosis. Ketosis
212 was relatively low and ranged between 0.03 to 15 mmol/L (Table 2). Only Tan-Shalaby
213 (2016) investigated whether patients achieved the glucose ketone index⁽³⁰⁾ that has been
214 proposed to monitor the efficacy of metabolic therapy⁽³⁹⁾, however, patients did not
215 achieved values predicted for therapeutic effects (<1.0)(Supplementary Document D).

216 Adverse events

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

1
2 220 16 reported fatigue, 12 constipation, 8 diarrhoea, 8 hyperuricemia and 4 vomiting. One
3 221 study reported hunger in 2 and craving for sugar in 5 out of 12 patients ⁽³¹⁾. Hyperkalaemia
4 222 and hypokalaemia were reported in 2 patients. Also, 2 patients experienced
5 223 leukocytopenia. Adverse events such as oesophagitis, anaemia, hypomagnesemia, pedal
6 224 oedema, halitosis, hypoglycaemia, hyperlipidaemia and deep vein thrombosis were
7 225 observed only once across studies.

11 226 Quality of life

12 227 Three studies assessed the QoL with validated European Organization for Research and
13 228 Treatment core quality of life questionnaire ^(30; 32; 37). No consistent results were reported.

14 229

18 230 Discussion

19 231 From hypothetical conjecture based on academic modelling supported by animal and
20 232 cellular studies, KD have a sound theoretical bases for suppressing tumour growth ^{(11; 20;}
21 233 ²¹⁾. However, strong conclusive evidence in clinical practice is still lacking.

22 234 Current studies demonstrated that patients on KD lose weight. This is of concern for
23 235 sarcopenic and malnourished patients as body composition and nutritional status have
24 236 been shown to influence clinical outcomes ^(25; 40). However, most of the studies did not
25 237 monitor energy intake, and it is very likely patients followed a hypocaloric diet. **This was**
26 238 **demonstrated in two studies ^(32; 37) and possibly attributed to self-administrated diet and**
27 239 **limited diet monitoring.** Also, it is widely accepted that body weight is a weak predictor of
28 240 changes in health status ⁽⁴¹⁾, as patients might lose fat but not muscle mass ⁽³⁷⁾. Hence,
29 241 further studies of KD that control energy and macronutrient intake and measure body
30 242 composition are required.

31 243 **This review found a low adherence to KD possibly due to a number of factors. The**
32 244 **proportion of macronutrients influence ketosis. Studies followed variable F:CHO+P ratio,**
33 245 **and thus the ketosis may have been affected by levels of carbohydrate and protein. It was**
34 246 **originally proposed that carbohydrate should be maintained below 20g per day but no data**
35 247 **exist to define what level of carbohydrate represents a threshold for maintenance of**
36 248 **ketosis ⁽²⁰⁾. Studies in this review used a great variation of carbohydrate, reaching to 70g**
37 249 **per day. Also, it has been suggested that a very high protein intake may counteract the**
38 250 **level of ketosis by providing glucogenic amino acids for production of glucose when the**

1
2 251 level of protein exceeds the normal non-starvation protein turnover⁽²⁰⁾. Hence, the
3 252 carbohydrate and protein ratio may explain a low ketosis.

5 253 Furthermore, the maintenance of ketosis and adherence to KD are very likely underpinned
6 254 by limitations in the delivery of the diet and monitoring. Schwartz (2015) suggested that
7 255 patients require weekly contact with a dietitian⁽³⁸⁾. However, most of the studies tested
8 256 self-administrated diet and had little control over the food selection, energy and nutritional
9 257 composition. In contrast, Zahra (2017) provided tailored meals but the compliance was still
10 258 poor, indicating that delivery of the diet represents only one contributor to adherence. The
11 259 author concluded that patients found a 4:1 fat to carbohydrate ratio unpalatable⁽²⁹⁾.

12 260 Possibly, palatability plays a crucial role and patients are unlikely to follow a restricted diet
13 261 for a prolonged period of time. There were no obvious differences in adherence between
14 262 studies with the original 4:1 KD and those using a Modified Atkins diet or similar
15 263 macronutrient ratio. The evidence indicates that following the diet is difficult for patients,
16 264 especially incorporating the diet into family life⁽³²⁾. Schmidt (2011) suggested that
17 265 patient's motivation is critical⁽³²⁾ and that diet would only be a good option in highly
18 266 motivated patients.

19 267 Furthermore, the adherence is closely related to adverse events. It is difficult to
20 268 differentiate between events related to treatment and those specific to the diet, especially
21 269 in very advanced cancer. Constipation, diarrhoea and fatigue were the most frequently
22 270 reported problems. Due to low dietary fibre content, patients following a KD are likely to
23 271 experience constipation. Studies that reported on dietary fibre showed a range between
24 272 7.9 g - 12.5 g/day, while 20-30 g/day is recommended⁽⁴²⁾. On the other hand, if a
25 273 substantial proportion of fat in a diet, is not introduced gradually, it might lead to diarrhoea
26 274⁽⁴³⁾. Also, a decrease in carbohydrate intake and simulation of fasting may lead to fatigue.
27 275 These adverse events were more frequent in the first four weeks on a diet, indicating that
28 276 time for adaptation is required⁽³²⁾.

29 277 Concerns about acidosis, kidney and hepatic functional impairment have not been
30 278 confirmed. Two studies reported hyperuricemia, which needs further investigation. Many
31 279 adverse events were reported as single cases, indicating the importance of considering
32 280 comorbidities when prescribing the diet⁽³⁵⁾.

33 281 Mixed results were observed in blood parameters, tumour, quality of life and survival. No
34 282 clear trend in changes of glucose and lipids could be concluded. Inverse correlation
35 283 between glucose and ketones level was demonstrated only in two studies^(33; 37). Tumour

1
2 284 responses were better in patients with early stage of disease^(32; 37) or with low-grade
3 285 tumours when the ketogenic diet was used as a sole therapy⁽³⁴⁾. Patients with stable
4 286 disease or partial remission were able to achieve 3-fold higher ketosis than patients with
5 287 more progressive disease⁽³³⁾. Some patients achieved outstanding results on tumour
6 288 stability and survival while others progressed. Most of the studies included mixed cancer
7 289 populations, and thus it is unclear what cancer site could benefit from the diet the most.
8 290 However, positive responses were clearly observed in patients with brain tumours. The
9 291 quality of life parameters slightly improved, worsened or remained unchanged. However,
10 292 due to high level of bias, a small number of patients who had a high level of adherence to
11 293 the diet, and no control group, conclusions are difficult to ascertain from the available data.

18 294 **Conclusion**

20 295 Current studies represent preliminary evidence and show that the KD is potentially feasible
21 296 and does not cause life-threatening events in patients with cancer. However, adherence is
22 297 low and possibly linked to a limitation in diet delivery, the lack of monitoring and follow up.
23 298 A high level of heterogeneity among studies prevents the formulation of conclusions. To
24 299 develop the evidence base for the use of KD in clinical practice, high quality control trials
25 300 are required.

33 302 ***Conflict of interests, source of funding and authorship***

35 303 The authors declare that they have no conflicts of interest. No funding has been received.
36 304 Non-financial support has been provided by the University of Manchester.

39 305 ***Transparency declaration***

41 306 The lead author affirms that this manuscript is an honest, accurate, and transparent
42 307 account of the study being reported, that no important aspects of the study have been
43 308 omitted and that any discrepancies from the study as planned (and registered with
44 309 PROSPERO) have been explained. The reporting of this work is compliant with PRISMA
45 310 guidelines.

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24 61; 62; 63; 64; 65; 66)
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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram

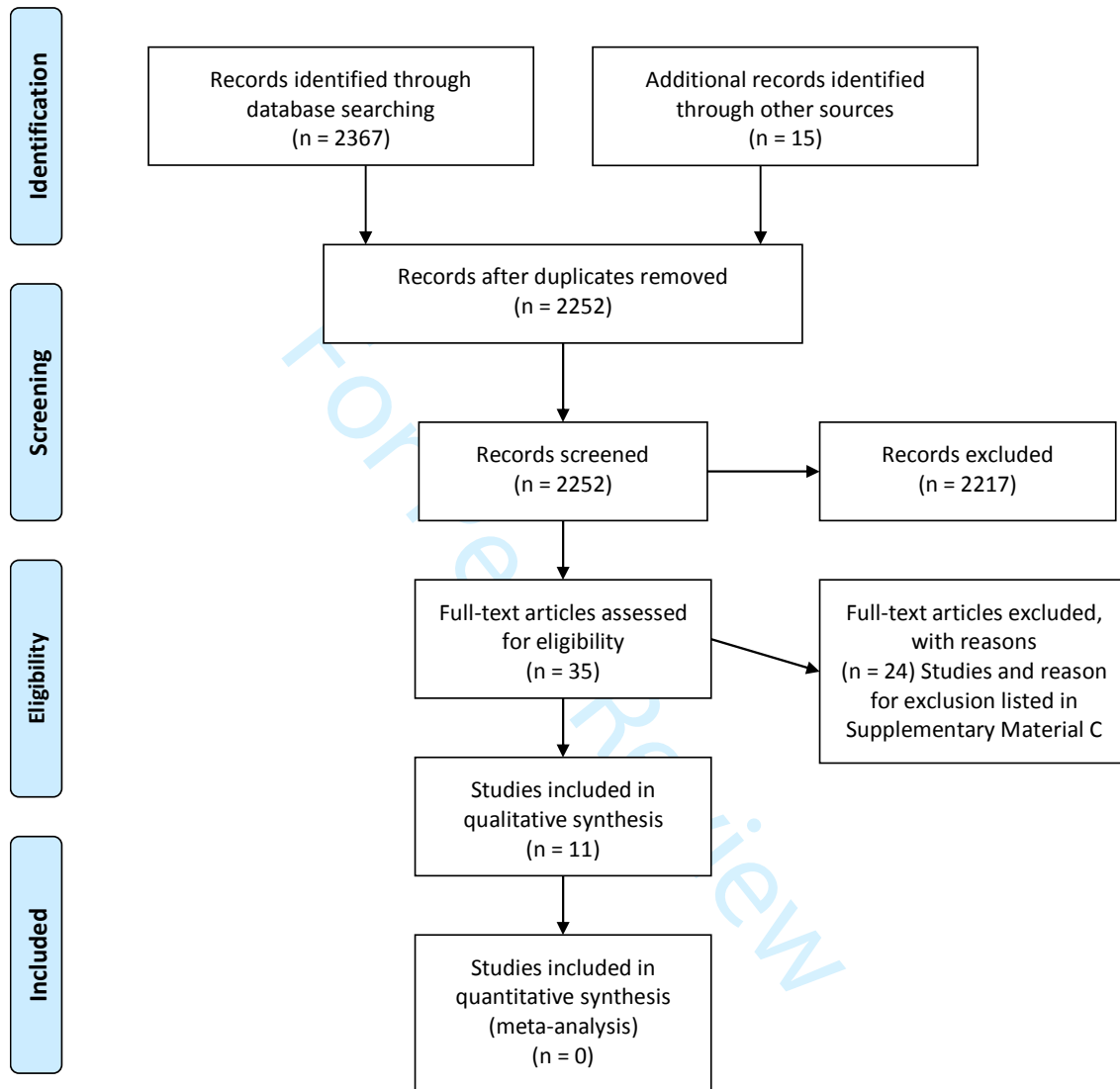


Table 1 Studies characteristics

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

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3	Strowd	-3.4±6.5 kg	NR	NSD	NSD in	NSD in creatinine	5 (63%) at least 50%	
4	2015				cholesterol, LDL,		reduction in seizure	7/8
5					HDL, TG		frequency, 4 seizures free	
6								
7	Klement		sig FM ↓ FFM ↑			NSD in CRP, IGF-1,		
8	2016	↓ NR	relative to body	NSD	NSD in LDL, HDL,	TSH, creatinine,	5 tumour regressions, 1	6/6
9			weight		cholesterol, TG	HbA1c, insulin, ALT,	progressed	
10						AST		
11								
12	Schwartz	NR	NR	1 after discharge ↑ >	1 cholesterol ↑ to		progressed	1/2
13	2015			80 mg/dl, 1 not below	281 at 6 weeks,	NR		
14				80 mg/dl	after 12 weeks to			
15					252, LDL ↑ to 197			
16					after 6 weeks, to			
17					182 at 12 weeks			
18								
19								
20	Toth	-13 kg	NR	decrease	↑ lipid enzymes,	normal renal, liver,	↓ tumour markers, stable	1/1
21	2016				slight ↑	thyroid, inflammatory	on diet, after 24 months	
22					cholesterol, LDL,	markers	progressed	
23					TG low			
24								

27 ALT- alanine aminotransferase, AST- aspartate aminotransferase, BHB -beta hydroxy butyrate, CRP - C reactive protein, FM - fat mass, FFM - fat free mass, HDL- high
 28 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-
 29 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 unnecessarily 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 outcomes	Cannot tell	No	Yes	NIL
Artzi 2017	Prospective cohort study	Yes	No	No	No	Yes	No	Yes	Yes	Brain metabolism changes	CI 95% not given	Cannot tell	Yes	Yes	NIL
Schmidt 2011	Prospective 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

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3 **Supplementary Document C Excluded studies**
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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

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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

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6	Champ	CHO 30-50 g/day 8%,	Vegetable, meat,	Biweekly in serum,					
7	2014	F 77%, P 15%,	fish, egg, cream, nuts	daily in urine	85.7kg	Diet	NR	NS	3 to 12
8			and oils	(NR/5.6/14.1		software			months
9				mg/dl)					
10									
11	Strowd	CHO 20g/day	High-fat foods.	Biweekly then	78.8 ±18.3 kg	NR	NR	NR	Median
12	2015		multivitamin, vitamin	weekly, NR	25.7±3.5kg/m ²				13.2 months
13			D, calcium						(range 2-24)
14									
15									
16		F:CHO+P ratio 0.8:1							
17		to1.8:1, mean EI	Olive, coconut oil,						
18	Klement	2043.5 kcal, CHO	butter, ghee, fatty	Daily in urine, 3x in	82.02 kg	Food	Yes	NS	32 to 73+
19	2016	32.3g/day, P	fish, cheese, meat	blood, (0.03 to 1.31		diaries			days
20		100.2g/day, F 166.7g/	and non-starchy	mmol/l)					
21		day	vegetables						
22									
23									
24									
25	Schwartz	F:CHO+P ratio 3:1, P	Commercial drink	Daily in blood,	27 kg/m ²	Phone	Yes	12	4 to 12
26	2015	0.6 g /kg body weight		(score 2 to 4)	24.3 kg/m ²	calls			
27									
28									
29						Personal			
30	Toth	F- P ratio 2:1	Meat and fat, root	Daily in urine,	78 kg	visits,	NR	NS	22.5
31	2016		vegetables < 30%	(score 1+ to 3+)	25.5 kg/m ²	phone			months
32						calls,			
33						emails			
34									
35									

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