**The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas. A systematic review.**

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**SUMMARY POINTS**

* This article systematically reviews the evidence for the effectiveness and acceptability of different ketogenic diets (KD) in the therapeutic management of patients with gliomas.
* Six studies have been published since 1995, conducted in the USA and Europe (n=39).
* All studies are case series evidence, the lowest position in the evidence hierarchy. However, at present this is the only evidence available to inform decisions regarding the implementation of KDs for gliomas.
* Minimal adverse events were reported, suggesting KDs to be safe in this population.
* The evidence for effectiveness and acceptability of various KDs is insufficient to suggest they have a therapeutic effect in the management of gliomas; therefore further high quality research is needed.
* Key areas for future research include:
  + A pragmatic feasibility study to inform future randomised control trial design.
  + High quality randomised control trials to determining if KDs are effective in the management of glioma.
  + A health economic assessment to establish efficiency, clinical effectiveness and value of the intervention.

**ABSTRACT**

Introduction: We performed a systematic review of the evidence for effectiveness and acceptability of different ketogenic diets in the therapeutic management of gliomas.

Methods: The search strategy included searches of seven electronic databases. Data extraction and quality assessment were undertaken independently by two authors.

Results: No randomised clinical trials were identified. Six studies (n=39) met the eligibility criteria for this review - all were case series or reports and therefore at high risk of bias. All studies reported overall or progression free survival; however the effectiveness of KD interventions could not be established. Dietary acceptability was not reported.

Conclusion: The effectiveness and acceptability of KDs in the management of gliomas is unknown and high quality randomised controlled trials are needed.

**PROSPERO protocol registration number**

CRD42017056752

**Key words**

Ketogenic diet, glioma, glioblastoma, systematic review.

**BACKGROUND**

*Description of the condition*

Primary brain tumours affect 7.14 per 100,000 of the worldwide population each year [1], with gliomas being the commonest form of malignant brain tumour, affecting 3-5 people per 100,000 each year [2]. Despite current treatment options including surgical resection, radiotherapy and chemotherapy these tumours remain incurable and the prognosis is poor.

*Description of the intervention*

Warburg first recognised that tumour cells rely on glucose for energy in 1926 [3]. Over the decades the Warburg theory has been developed further, leading to the hypothesis that switching gliomas’ energy source from glucose to ketones may result in cancer cell death [4]. One mechanism for achieving this is by targeting tumour energy metabolism with the ketogenic diet (KD); a high fat, low carbohydrate diet, which results in the production of ketones as a primary energy source, whilst minimising glycolysis through glucose restriction [5].

KDs are perceived as unpalatable and their assessment in patients with poor survival outcomes has therefore been limited. However, following the success of the classic 4:1 KD (4g fat for 1g of carbohydrate and protein combined, approximately 90% total energy from fat) in paediatric epilepsy, dietary variants have been developed that are designed to be more palatable and easier to implement, with fewer side effects [6].

*Why this review is important*

A systematic review and meta-analysis of the anti-tumour effects of KD in mice demonstrated a prolonged survival for the KD groups compared to standard diet (mean survival time ratio= 0.85 (95% highest density interval = [0.73, 0.97]); hazard ratio = 0.55 (95% highest posterior density interval = [0.26, 0.87])) [7]. To our knowledge no such review exists for human studies and a review of the best current evidence is required to inform decisions about service provision and the design of future clinical trials.

**Research question and aim**

Aim: To review the evidence for effectiveness and acceptability of different KDs in the therapeutic management of patients with gliomas.

**METHODS**

The protocol for this systematic review was registered with PROSPERO (identification number: CRD42017056752).

The PICO table below illustrates the review question and inclusion criterion (population, intervention, outcomes, setting and study design). As all study designs were considered, a comparator arm was not essential (see table 1).

|  |  |  |
| --- | --- | --- |
| Table 1: A PICO table illustrating the systematic review question and criterion. | | |
| Review question | Is there a role for KDs in the therapeutic management of adult and paediatric gliomas? | |
| Population | Adults and children with glioma tumours following a KD. | |
| Intervention | Any form of KD, with KD defined as a diet that is designed to produce ketones. | |
| Outcomes | Objective or self-reported measures are acceptable for the following outcomes: | |
| Primary outcomes:   * Overall survival * Progression free survival | Secondary outcomes:   * Adverse events * Retention rates * Quality of life * Acceptability * Tolerability * Compliance * Duration of KD * Time of dietary commencement (in relation to treatment pathway) * Ketone levels * Glucose levels |
| Setting | Primary, secondary or tertiary healthcare. Inpatient, outpatient or community settings. | |
| Study design | All. | |

No restriction was placed on year of study or publication status. The search was limited to English language publications.

**Search strategy**

A four-part search strategy was implemented to identify suitable studies.

*Electronic searches*

The following electronic databases were searched.

1. EMBASE
2. PubMed
3. Cochrane Library
4. CINAHL Plus
5. MEDLINE
6. SCOPUS
7. Web of Science

The primary search was undertaken on 25th January 2017, with updates identified until 18th August 2017 (see appendix 1 for example search strategy)

*Hand searches*

References of the included studies were hand searched to identify other possible studies.

*Study registries*

The following study registries were searched:

1. ClinicalTrials.gov
2. The World Health Organisation International Clinical Trials Registry Platform
3. UK Clinical Trials Gateway
4. International Standard Randomised Controlled Trial Number Register (ISRCTN)
5. National Institute of Health Clinical Trials Registry
6. National Research Register Projects Database Achieve
7. PROSPERO

The search was undertaken on 21st March 2017, with updates identified until 18th August 2017.

*Other resources*

Conference abstracts and posters were included in the search to identify recent studies undertaken that may not be published or are ongoing.

*Screening of included studies*

Duplicate references were removed from the search results. Pre piloted inclusion criteria were applied to titles and abstracts identified in the search results. Full text was obtained for studies identified for potential inclusion and inclusion criteria were re-applied. Following this, an expert in the field (Dr A C Scheck) was also contacted to identify any studies that were shortly due for completion or publication.

*Reporting results of searches*

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRIMSA) flow diagram was adopted to document the number of references located from databases and other sources, the number of duplicates removed, records screened, records excluded, full text articles screened, full text articles excluded with reasons and the number of studies included in the final review [8].

**Data extraction and quality assessment**

Two authors (KJM and NS) independently extracted data using a pre piloted data extraction form. Any discrepancies were discussed between the two authors in the first instance. A third author (MDJ) was available for consultation should disagreements have occurred.

Although all study types were permitted for inclusion in the review, only case studies and case series were identified. Therefore the Institute of Health Economics (Canada) Case Series Quality Appraisal Checklist was selected as the appropriate quality assessment tool [9]. Again, the tool was applied by KJM and NS.

**RESULTS**

**Description of studies**

*Results of the search*

The electronic search identified 2380 records, and another 2 were identified by searching the references of included studies. After removing duplicates 1713 records remained. Following the screening of titles and abstracts 19 remained eligible for inclusion. These studies underwent a full text review, following which a further 13 studies were excluded due to inappropriate interventions [10,11], inappropriate populations [7,12–15] and inappropriate outcome measures [16–20]. Therefore 6 studies met the eligibility criteria for this review [21–26] (figure 1). No further studies were identified from the expert in the field.

Figure 1: PRISMA Flow Diagram

Records excluded  
(n = 1694)

Records screened  
(n = 1713)

Records after duplicates removed  
(n = 1713)

## Identification

## Eligibility

## Included

## Screening

Additional records identified through other sources  
(n = 2)

Records identified through database searching  
(n = 2380)

Full-text articles assessed for eligibility  
(n = 19)

Full-text articles excluded   
(n = 13)

Inappropriate intervention (n = 2)

Inappropriate population (n = 5)

Inappropriate outcomes (n=6)

Studies included in qualitative synthesis  
(n = 6)

Studies included in quantitative synthesis (meta-analysis)  
(n = 0)

*Included studies*

Six studies have been published since 1995, conducted in the USA and Europe. Population sample size varied between 1 to 20 participants, with a variety of KD interventions. Table 2 provides a summary of the study characteristics.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2: Study characteristics | | | | | | | | | | Survival data (median [range]) | |
| Study | **Location** | **Methods** | **Primary objective** | **Number of patients** | **Age** (years) | **Diagnosis** | **Dietary intervention** | **Dietary duration** (months, [range]) | **Follow up** (months, [range]) | **Overall survival** | **Progression free survival** |
| Champ et al., 2014 | USA | Retrospective case series | Safety | n=6 | 34-62 | Grade III-IV glioma | 50g CHO KD | 3-12 | 5-20.3 | 27-88 weeks (range only) | 45 weeks \* |
| Nebeling et al., 1995 | USA | Prospective case series | Nutritional status, tumour metabolism and QoL | n=2 | 3-8.5 | Grade IV anaplastic astrocytoma spinal cord; grade III cerebellar astrocytoma | MCT KD | 2-14 | 2-24 | 0 deaths reported | 0 progressions reported |
| Rieger et al., 2014 | Germany | Prospective case series | Safety and tolerance | n=20 | 30-72 | GB | 60g CHO KD, fermented yoghurt drinks, two plant oils | 6-42 | 1.2 (median only) | 32 weeks (6-86+ weeks) | 5 weeks (3-13 weeks) |
| Schwartz et al., 2015 | USA | Prospective case series | Unclear | n=2 | 52-55 | GB | ER 3:1 KD | 1-3 | 1-3 | No data | 8 weeks (4-12 weeks) |
| Strowd et al., 2015 | USA | Retrospective case series | Safety and clinical impact | n=8 | 28-54 | Grade II-IV glioma | 15-20g CHO MAD | 2-24 | 13.2±8 (mean, S.D.) | 0 deaths reported | No data |
| Zuccoli et al., 2010 | Italy | Retrospective case report | Unclear | n=1 | 65 | GB | ER 4:1 KD | 1.8 | 25 | No data | 43 weeks |

**Risk of bias in included studies**

All six studies were at high risk of bias and a summary of the quality assessment can be found in table 3.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 3: Summary of quality assessment of included studies | | | | | | | | | | | | | | | | | | | | |
|  | **Objectives** | **Design** | | | **Population** | | | **Interventions and co interventions** | | **Outcome measure** | | | | **Statistical analysis** | **Results and conclusions** | | | | | **Competing interests/ sources of support** |
| Study | Aim/ objectives | Prospective | Multicentre | Consecutive recruitment | Participant characteristics | Eligibility criteria | Similar point of trial entry | Clear intervention | Clear additional interventions | OM established priori | Blinded assessors | Appropriate methods | OM pre and post intervention | Appropriate tests | Follow up period | Losses reported | Estimates of random variability | AE reported | Supported conclusions | Reported upon |
| Champ et al., 2014 | ✓ | 🗶 | U | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓🗶 | U | ✓ | U | U | ✓ | ✓ | ✓🗶 | ✓ | ✓ | ✓ |
| Nebeling et al., 1995 | ✓ | ✓ | 🗶 | U | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | U | ✓🗶 | U | U | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ |
| Rieger et al., 2014 | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | U | ✓🗶 | U | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Schwartz et al., 2015 | ✓🗶 | ✓ | 🗶 | U | ✓ | ✓ | ✓ | ✓ | ✓ | ✓🗶 | U | ✓ | ✓ | U | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ |
| Strowd et al., 2015 | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓🗶 | ✓ | ✓ | ✓ | 🗶 | U | 🗶 | U | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Zuccoli et al., 2010 | 🗶 | 🗶 | 🗶 | U | ✓ | 🗶 | U | ✓ | ✓ | 🗶 | U | ✓🗶 | U | NA | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ |

**Effects of interventions**

*Critical outcomes*

Overall survival

Four studies reported overall survival (n=36). Follow up ranged from 6 weeks to 91 weeks. Two studies comprising 10 patients reported no deaths [23,26]. Two studies comprising of 22 patients reported survival ranging from 6 to 88+ weeks [21,22]. Survival can be related to diagnosis and dietary intervention in table 2.

Progression free survival

Five studies reported progression free survival (PFS) (n=30). Time to progression ranged from 3 to 45 weeks in four studies [21,22,24,25]. One study comprising of 2 patients reported no progression following 62 weeks on diet, at time of writing (n=1); however, PFS for the second patient was not reported [26]. PFS can be related to diagnosis and dietary intervention in table 2.

*Important outcomes*

Adverse events

All studies reported adverse events (n=39). The most frequently reported adverse effects related to KD interventions were weight loss [21-25], ranging from -2.2% body weight [22] to -13% body weight [25] and increased cholesterol [24,26]. Other adverse effects reported in low numbers were deep vein thrombosis [21], grade III leukopenia [22], lymphopenia [25], hyperuricemia [25], hypoproteinemia [26].

Dietary retention rates

The retention rate could be determined for three studies (n=24), all undertaken prospectively using a defined protocol, which ranged from 50-100% [22,24,26]. Retention was determined at 8 weeks (n=2) [26], 12 weeks (n=2) [24] or at point of tumour progression (n=20) [22] (median PFS 5 weeks, range 3-13 weeks). Reasons for withdrawal from diet included tumour progression (n=1) [24] and negative impact on quality of life (n=3); however no validated tool was documented [22].

Quality of life

No studies reported quality of life using appropriate objective or subjective measures.

Acceptability

No studies reported dietary acceptability using appropriate objective or subjective measures.

Tolerability

Two studies reported dietary tolerability (n=18). Grade I constipation was reported at dietary initiation (n=2), grade I fatigue (n=4) during radiotherapy and grade II fatigue (n=1) during 30% energy restricted 30-50g carbohydrate KD [21]. Gastrointestinal assessment reported diarrhoea at a mean intensity of <1 (weak), constipation at a mean intensity of <1 (weak), hunger of mean intensity of >1 but <2 (weak to moderate) and demand for glucose mean intensity of >1 but <2 (weak to moderate), using a non-validated questionnaire (n=12) [22].

Compliance

Three studies reported dietary compliance (n=24). Maintenance of ketosis was used as a surrogate for compliance in two studies [24,26], whilst patient self-reporting demonstrated compliance for 6.8 days per week (n=20) [22].

Ketone levels

Five studies reported ketosis (n=24). Three studies reported serum ketosis (n=6), with levels between levels of 0.3mmol/L\* to 7mmol/L (n=4) [21,24] and maintenance of serum ketosis was reported by one study (n=2) [26]. Urinary ketosis was reported by two studies (n=14). One study reported urinary ketones between 1.5-2.5mmol/L during first 3 weeks of diet (n=1) [25]. In the other, urinary ketosis achieved at least once in 92% participants (n=12/13) and when assessing all urinary measurements from 12 participants, ketonuria was present in 73% of cases [22]. Methodology and frequency of testing was not consistent between studies.

\* indicates reported units have been converted to mmol/L from mg/dl for comparison.

Glucose levels

Five studies reported serum glucose levels (n=18). Three studies (n=14) reported a decrease in serum glucose during diet compared to pre diet levels. However, levels varied from a mean non fasting serum glucose of 7.9mmol/L\* pre diet (no S.D.) to 4.7mmol/L\* (no S.D.) (n=4) [21], to 7.5mmol/L pre diet decreasing to 3.5mmol/L during diet (n=1) [25], with a less extreme response noted in one study (5.5±1.2mmol/L\* pre diet to 5.1±0.5mmol/L\*during diet; n=9) [22]. One study reported serum glucose levels during diet only (3.5-5.5mmol/L; n=2) [26] and one study reported serum glucose could not be maintained below the target of 4.4mmol/L\* (n=2) [24].

\* indicates reported units have been converted to mmol/L from mg/dl for comparison.

**Ongoing trials**

*Results of search*

Eighteen records of ongoing trials were identified within study registries. After removing duplicates 12 records relating to 12 individual trials remained (total participant population of n=265), all of which were eligible for this review [27–38]. Table 4 summarises characteristics of the 12 ongoing clinical trials.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Table 4: Summary of ongoing clinical trials | | | | | | |  |
| Study | **Location** | **Population condition** | **Target sample size** | **Dietary intervention(s)** | **Primary outcomes** | **Secondary outcomes** | **Expected date of completion** |
| Ghodsi , 2012 | Iran | Post Sx, CRT GB | 20 | ER MCT KD (50% MCT, ER to 25kcal/kg/day) | Survival | Quality of life | Unknown |
| Guimaraes Santos & Pereira da Fonseca, 2016 | Brazil | Recurrent GB | 30 | KD v control with intranasal administration of perillyl alcohol | Tumour size | Anthropometry | Unknown |
| Jameson, 2014 | New Zealand | Newly diagnosed GB | 20 | KD (<30g CHO/day) | PFS | Ketosis  Treatment compliance  Dietary compliance  Food satisfaction  SGA  Adverse events | Unknown |
| Martin & Jenkinson 2017 | UK | Newly diagnosed GB | 12 | MKD (5% CHO, 80% fat) v MCT KD (10% CHO, 75% fat [30% MCT]) | Retention | Enrolment  Long term retention  Dietary adjustments  Self-reported compliance  Calculated compliance  MCT compliance  Ketosis  Dietetic time  Protocol refinements  Sample size estimations  Quality of life  Food acceptability  Gastrointestinal side effects  Biomarkers  Anthropometry  Completeness of data | March 2019 |
| Klein, 2014 | USA | Recurrent GB | 6 | ER 4:1 KD (1600kcals/day) v standard diet | Overall survival  PFS  Adverse events | Tolerability | August 2017 |
| Klein, 2016 | USA | Newly diagnosed GB | 6 | ER 4:1 KD (1600kcals/day) | Safety | Efficacy  Tolerability | May 2017 |
| Rieger & Steinbach, 2012 | Germany | Recurrent GB | 50 | ER KD with IF (<60g CHO/day) v standard diet | PFS | Feasibility  Safety  Tolerability  Overall survival  Seizure frequency  Ketosis  Quality of life  Depression  Attention  Response | October 2017 |
| Scheck, 2014 | USA | Newly diagnosed GB | 14 | 4:1 KD reduced to MAD post CRT | Adverse events | Overall survival  PFS  Quality of life | March 2017 (study ongoing, not recruiting) |
| Schwartz, 2012 | USA | Newly diagnosed GB | 12 | ER KD  (20-25kcals/kg/day) | Tumour size | None stated | July 2017 |
| Song, 2016 | China | Recurrent GB | 60 | KD v standard diet | Adverse events | Chemotherapy sensitivity  Overall survival  Ketosis  Quality of life | December 2018 |
| Strowd, 2014 | USA | Post Sx, CRT GB | 25 | MAD with IF | Feasibility | Tolerability  Biological activity  Glucose levels  Ketosis  Anthropometry  Seizure frequency | November 2018 |
| Vaisman, 2010 | Israel | Recurrent GB | 40 | KD v standard diet | Tumour size | Performance scale  Quality of life | March 2011 (last updated March 2010) |

**DISCUSSION**

**Summary of main results**

This systematic review identified no high quality prospective studies assessing KD for glioma, but did identify a number of small randomised controlled trials that are currently on-going. All six published case series included in this review reported overall or progression free survival, however due to the limited sample sizes (ranging from one to twenty participants) and the absence of a control group it is not possible to make any conclusions as to the effectiveness of the KD interventions.

Adverse events were consistent across the majority of studies, predominately being weight loss and raised cholesterol. However, two studies adopted an energy restricted KD, following which weight loss would be expected [24,25]. The significance and clinical impact of weight loss would need to be considered and could be managed through non-energy restricted, non-fasting regimes supported by a trained dietitian [26]. The impact of KD on cholesterol profiles should also be considered within the context of a disease that has poor long-term survival. Whilst two studies reported an increase in cholesterol [24,26], one study, conflictingly reported cholesterol to reduce over the course of the diet [22]; therefore requires further investigation.

Retention rates on diet varied from 50 to 100%, however only three studies utilised a study protocol with predetermined duration for the dietary intervention [22,24,26]. As sample sizes of these studies range from two to twenty participants the external validity of such data is questionable. No studies reported quality of life or dietary acceptability using the appropriate objective or subjective measures and are therefore subject to performance bias. Future studies should consider the inclusion of validated measures to assess quality of life and dietary acceptability.

Dietary compliance was inconsistently measured, with two studies citing the presence of serum ketones as a marker of compliance [24,26], and one study using self-reported measures [22]. Both methods have their limitations; including selection bias with eligibility criteria requiring patients to be compliant with the diet prior to recruitment [24] and reporter bias from self-reported measures [22]. Due to diverse methodologies, it is not possible to determine which diet is easier for participants to comply with.

A trend for the decrease in serum glucose levels, whilst adhering to a KD, can be noted across the studies, with glucocorticoids having a negative impact on levels. However, the clinical impact of this cannot be determined from the results of the studies so far. Five studies measured ketones in either urine or serum, however due to different methods no comparisons can be made between diets.

This review also identified twelve ongoing studies, five of which are randomised control trials (RCT). Three RCTs may be suitable for future meta-analysis [28,29,31]. These studies have comparable populations, outcome measures, control groups and similar dietary interventions, but further dietary and methodological details would be required to assess the appropriateness of such an analysis. The planned recruitment figures remain small and the trials are underpowered to demonstrate effectiveness. A multi-centre RCT or the ability to undertake a meta-analysis is required.

**Potential biases in the review process**

Thorough database searches were performed to identify studies suitable for this review. Application of the eligibility criteria to the research results identified six studies for inclusion. Given the relative novelty of KD in gliomas, a low number of editorials were expected. As the search strategy was first piloted and the results of the search strategy supplemented by hand searches, it is unlikely that relevant studies were missed, further confirmed through contact with an expert in the field. Therefore conclusions drawn from the review are based upon all available evidence.

A key strength of this review lies in the quality assessment of included studies. The Institute of Health Economics (IHE) (Canada) Case Series Quality Appraisal Checklist [9] is the only validated quality appraisal tool for assessing the methodological quality of case series [9,39]. The tool was updated to include assessor annotations specific to this review as recommended by the tools authors [9], to aid the quality appraisal process. The tool does not provide a scoring system in which study quality may be distinguished as high or low, therefore it was not possible to strictly assess the confidence of cumulative evidence. As such, a narrative approach was taken in this review. No studies fulfilled the full study design criteria of the quality assessment tool.

Three studies utilised a study protocol enabling the repetition of their methods [22,24,26]. Of these, one study author [24] provided the trial protocol and there appeared to be no suggestion of selective reporting bias.

One study included a retrospective control group [21], however failed to statistically or descriptively compare the control group to the dietary intervention group. The control group was also unlikely to represent the population due to convenience sampling methods and eligibility criteria requiring variables not held within the records, thus creating selection bias. Therefore this study design was also considered a case series.

A meta-analysis was not undertaken due to the heterogeneity of the study populations, methods, outcomes and bias stated previous. The overall measure of treatment effect would be misleading given studies were not powered to determine treatment effect. Study populations varied from newly diagnosed grade III or IV gliomas to recurrent gliomas and the KD was administered at different time points in the treatment pathway. Participants also received a wide variety of oncology treatments whilst following KD. The KD interventions also varied, in terms of energy and carbohydrate restrictions, and types of dietary fats included. One study included fermented yoghurts and plant oils in addition to KD [22], therefore presenting difficulties when comparing KD outcomes. Ongoing studies may provide better quality data and synergy between protocols to allow for meta-analysis in future reviews.

**Implications for practice and research**

Due to the lack of high quality evidence it is difficult to justify the use of KDs in a clinical, non-research setting. Further research is required to explore dietary acceptability, cost effectiveness and clinical effectiveness, prior to implementation alongside the current standard of care in this population.

Key areas for future research include:

1. A pragmatic feasibility study to inform future randomised control trial design; with outcomes related to adverse events, retention rates, quality of life, dietary acceptability, tolerability and compliance, using validated measures, as adopted by the KEATING study [32].
2. Determining if KDs are effective in the management of glioma, through high quality RCTs. It will be important to consider which KD, if any, is beneficial and at what point in the treatment pathway. KD concurrent to chemoradiotherapy in animal models has proven to potentiate the treatment effects; however, this is yet to be replicated within glioblastoma patients. Testing clinical effectiveness for median overall survival, in a newly diagnosed glioblastoma population, would require approximately 600 participants and is therefore unlikely to be achieved. It may be practical to power studies to progression free survival or overall survival at 6 months to enable attainable recruitment figures.
3. A health economic assessment to establish efficiency, clinical effectiveness and value of the intervention, would be beneficial. Establishing quality adjusted life years would be of benefit to assess disease burden, in terms of quality and quantity of life gained by patients, if at all any.

**AUTHOR’S CONCLUSIONS**

This review is based on case series evidence, the lowest position in the evidence hierarchy. However, at present this is the only evidence available to inform decisions regarding the implementation of KDs for gliomas. Whilst the review has found minimal adverse events, suggesting KDs to be safe in this population, the evidence for effectiveness and acceptability of various KDs is insufficient to suggest they have a therapeutic effect in the management of gliomas. Further high quality research would be of benefit.

**FUTURE PERSPECTIVE**

Over the next 5 to 10 years we may see the field of KDs in gliomas expanding, following the publication of current ongoing studies. There will be the opportunity for meta-analysis presenting more robust evidence on the subject. However, it may be several years before large scale, RCT evidence is published exploring the effectiveness of KDs in gliomas.

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**CONTRIBUTIONS OF AUTHORS**

KJM designed and wrote the manuscript. MDJ, NS, AGM and CTS reviewed manuscript with suggestions. NS participated in data extraction and quality assessment.

**DECLARATION OF INTERESTS**

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\*\* Of considerable interest – These are the 6 case studies included in this systematic review.

**Appendix 1**: **Example Search Strategy – Medline (Ovid)**

1. (ketogenic or ketone or ketosis or carbohydrate restrict\* or low carbohydrate or high fat or Atkin\* or glyc\*emic or triglyceride\* or medium chain triglyceride\*).af
2. (central nervous system or brain or cerebral or spinal or spine).af
3. (cancer or tumo\*r or malignan\* or neoplas\* or carcinoma\*).af
4. 2 and 3
5. (glioblastoma\* or astrocytoma\* or glioma\* or ependymoma\* or oligodendroglioma\* or ganglioglioma\* or medulloblastoma\* or astrocytic\* or ependymal\*).af
6. 4 or 5
7. 1 and 6
8. Limit 7 to (English language and humans)