The Modified Ketogenic Diet in Adults with Glioblastoma: An Evaluation of Feasibility and Deliverability within the National Health Service

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ABSTRACT
There is an increasing interest in the use of the ketogenic diet (KD) as an adjuvant therapy for glioma patients. We assessed the tolerability and feasibility of a modified ketogenic diet (MKD) in patients with glioma, along with willingness of patients to participate in future randomized controlled trials. The study was undertaken in two parts; a patient questionnaire and evaluation of the diet. One hundred and seventy-two questionnaires were completed; 69% (n = 119) of the population reported MKD should be offered to patients with glioma and 73% (n = 125) would be willing to try MKD for 3 months. Six male patients with high grade gliomas tried the diet; 4 completed the 3-month feasibility period. Ketosis was achieved in all patients. The only gastrointestinal side effect was constipation (n = 2). Minimal changes were observed in weight, body mass index, fat mass and cholesterol profiles. MKD was well tolerated, with few side effects and is deliverable within a financially viable, NHS service. There is a high level of interest in the diet within the glioma patient community to ensure adequate recruitment for a clinical trial. Further studies are required to demonstrate efficacy and patient benefit before implementing a service.

Introduction
Gliomas are the commonest primary malignant brain tumor in adults. Despite current treatment for high grade gliomas, such as anaplastic astrocytomas and glioblastomas, including maximal surgical resection, radiotherapy, and temozolomide chemotherapy, the overall survival remains poor, with 27% of glioblastomas surviving beyond 2 years and a median survival of 12–14 months (1,2). Over the last 10 years, several trials of newer chemotherapy agents (e.g., RTOG 0825 – Bevacizumab trial (3)) and targeted therapies (e.g., CENTRIC – Cilengitide trial (4)) have not improved the survival of patients with these tumors. Therefore, alternative treatment options are being explored. There is an increasing interest in using ketogenic diets (KDs) as an adjuvant treatment for patients with gliomas, with the James Lind Priority Setting Partnership in the Neuro-oncology community citing the effect of lifestyle factors (including diet) to be a top-10 research priority (5).

Gliomas are metabolically active tumors and rely on glycolysis for growth. In animal models, switching energy consumption away from glucose and onto ketone bodies has been shown to enhance survival (6), enhance radiotherapy sensitivity (7), improve chemotherapy signaling (8), and reduce peritumoural oedema (9). Whilst showing promising anti-tumor effects in animal models, effectiveness in humans has yet to be established through survival data.

Recent studies investigating the use of KDs in humans have focused on feasibility, safety, and efficacy. However, the current published evidence is based on case studies (10–13) and pilot trials (14). Assessing the effectiveness of interventions such as the KD in the NHS poses a number of challenges that need to be considered in order to inform trial design and feasibility.

One challenge is the lack of commissioned KD services in adult care settings, especially for brain tumor patients. There are few existing services in place to support a randomized control trial (RCT). However, without good evidence of cost effectiveness and efficacy a KD service would not be commissioned.

The second challenge is selecting the most appropriate KD to inform trial design. Previous studies have used a variety of KDs at various points in the treatment pathway, from post resection to palliation. The modified ketogenic diet (MKD) is the least
restrictive KD and induces ketosis through encouraging a high fat and low carbohydrate intake, without limiting protein, fluid, or energy intakes, as applied in other KDs. Therefore, it may be the most suitable KD for adults undergoing oncological treatments. There is no need for a fasting start or hospitalization to commence the diet (15), promoting ease of use and promoting cost-effectiveness. However, as with all KDs the MKD has notable side effects, predominantly gastrointestinal related (constipation, diarrhea, and reflux) and raised lipid profiles (16–18).

RCT evidence illustrates the beneficial effects of KD in paediatric epilepsy (19) and National Institute for Health and Care Excellence (NICE) supports the use of KD within the National Health Service (NHS) for paediatric epilepsy. However, the feasibility of delivering the MKD for adults with glioma, within the NHS is unknown. The aim of this study was to evaluate the tolerability and feasibility of MKD in patients with glioma within an NHS setting and patient willingness to participate in a RCTs.

**Materials and Methods**

Questionnaire development was undertaken by a multi-disciplinary team, including a Neurosurgeon, Neurologist, Biostatistician, and Dietitian at the University of Liverpool and The Walton Centre NHS Foundation Trust (WCFT). The questionnaire explored a patient’s baseline demographics, attitudes toward the use of the MKD for glioma, their willingness to try the diet, and willingness to participate in an RCT. The questionnaire contained information regarding the MKD and its use in glioma management, including a brief summary of the literature (animal models and case studies), foods permitted and excluded from the MKD, dietary duration, and additional monitoring required by the patient and clinician, to assist patients in making informed responses. The questionnaire was circulated to patients attending WCFT neuro-oncology clinics and distributed nationally, via brain tumor charity websites (Matthew’s Friends, Astro Brain Tumour Fund, The Brain Tumour Charity, braintrust) and their social media outlets.

Patients attending clinics at WCFT were offered the opportunity to try the MKD for a 3-month period. Patients were eligible if they met the following inclusion criteria: age ≥ 18 years, confirmed histological diagnosis of high-grade glioma who has undergone surgical resection. Exclusion criteria included prior use of a KD, kidney dysfunction, liver dysfunction, gall bladder dysfunction, metabolic disorder, eating disorder, diabetes (requiring medication), body mass index (BMI) ≤ 18.5 kg/m², and use of weight-loss medications.

Prior to commencing the MKD, baseline assessments were undertaken by the dietitian. Anthropometric measures (weight, height, BMI, mid arm muscle circumference, fat mass), biochemistry monitoring (renal, bone, liver function test (LFT), fasting lipid, fasting glucose, carnitine [only on initial screen]), and review of a 3-day habitual food diary were recorded. After commencing diet, patients were assessed by the dietitian at 6 and 12 weeks in clinic and by telephone reviews at weeks 1, 3, and 9. During clinical assessments anthropometry, biochemistry and food and ketone diaries were collected and analyzed. Telephone reviews were utilised for troubleshooting and dietary support. Dietary advice was tapered to the patient’s individual requirements.

The MKD comprised of 70% dietary fat, whilst dietary carbohydrate was limited to 20 g/day (3–5% total energy requirements), both of which were calculated using exchange lists. Protein sources were not restricted. All patients commenced the diet at home, without a fasting start.

Nutritional analysis of food diaries was undertaken using DietPlan 7© (Forestfield Software LTD, Horsham, UK). Dietary compliance and tolerance were monitored, along with changes to medications; however, medications were permitted to be altered in line with the clinician’s recommendations. Radiotherapy and chemotherapy were provided in line with the current standard of care.

Patients were provided with hospital literature regarding MKD, recipes, ketostix® (Bayer, Leverkusen, Germany), ketone diaries, and a 7-day MKD diet plan calculated by the dietitian, when commencing the diet.

Patients were instructed to check their urinary ketones twice daily for the first month, once per day for the second month, then twice weekly in the third month of diet, and record these figures in the ketone diary provided. Adequate urinary ketosis was defined as values ≥ 4 mmol/l (15).

At week 12, or upon exit of service if prior to this, patients completed a questionnaire to assess dietary tolerance, feasibility, willingness to participate in future trials, and to evaluate the dietetic service. For those patients who wished to continue with the MKD after 12 weeks, follow-up with the dietitian was offered every 3 months.

Descriptive statistics were used to summarize the results. For interest two sample-paired t-tests were used to compare anthropometry and biochemistry results pre-diet and at 12 weeks; however, the study was not adequately powered to address true significance. The study...
was also not powered to measure effectiveness at this stage.

The study was approved by WCFT Research, Development, and Innovation committee.

**Results**

**Patient Questionnaire**

One hundred and seventy-two questionnaires were completed – 50 at WCFT clinics and 122 online. Forty percent \((n = 69)\) of participants were male, 51% \((n = 88)\) female, 9% \((n = 15)\) not recorded, all aged between 16 and 69 years. Diagnoses were self-reported by the online population group; 30% \((n = 35)\) glioblastoma (grade IV), 25% \((n = 30)\) anaplastic astrocytoma, or oligodendroglioma (grade III), 43% \((n = 50)\) low grade glioma (grade II astrocytoma or oligodendroglioma and 2% \((n = 2)\) other. Fifty-eight percent \((n = 70)\) of the online population reported prior knowledge of KD, with charity websites \((n = 38, 39%)\) and online forums \((n = 22, 22%)\) being key information sources.

Sixty-nine percent \((n = 119)\) of the population reported MKD should be offered to patients with glioma. Seventy-three percent \((n = 125)\) of patients would be willing to try MKD for 3 months. There was no clear preference in the timing of when to start the diet: 25% \((n = 48)\) preferred to start the diet before surgery, 22% \((n = 42)\) immediately after surgery, 15% \((n = 28)\) after surgery during chemo-radiotherapy, 11% \((n = 22)\) after radiotherapy during chemotherapy and 27%, \((n = 52)\) after treatment during the monitoring phase.

Sixty six percent of patients \((n = 114)\) would be willing to participate in a clinical trial to investigate effectiveness and tolerability of the diet. Of these 54% \((n = 62)\) would still be willing to participate in the trial if it were randomized between MKD with standard care and standard care alone. Patients were also questioned about their motivators and barriers to participating in a clinical trial (Table 1).

**Feasibility Study**

Eight adults with high-grade glioma \((n = 7)\) glioblastoma (WHO grade IV); \(n = 1\) anaplastic astrocytoma (WHO grade III)) were referred for consideration of MKD. Six patients commenced diet \((n = 5)\) glioblastoma; \(n = 1\) anaplastic astrocytoma), whilst 2 patients declined the dietary intervention due to their poor performance status. There were no contraindications to MKD in any patient. Table 2 illustrates baseline patient demographics of the 6 patients who commenced MKD.

### Table 1. Motivators and barriers to trial participation.

| Motivating factors                                      | Number of responders, n(%) |
|---------------------------------------------------------|----------------------------|
| To help other adults with glioma                        | 120 (35)                   |
| To access the diet myself                               | 89 (26)                    |
| To get expert advice about the diet                     | 85 (25)                    |
| To improve quality of life                              | 25 (7)                     |
| Other                                                    | 18 (5)                     |

| Barriers to participation                               |                           |
|---------------------------------------------------------|----------------------------|
| Extra expense of travelling                             | 52 (22)                   |
| Extra burden on visiting a dietitian                     | 39 (17)                   |
| Extra expense of the diet                               | 39 (17)                   |
| Fear of side effects                                    | 25 (11)                   |
| Not applicable (no perceived burden)                    | 24 (10)                   |
| Not enough time to devote to the study                  | 16 (7)                    |
| Carer or family burden                                  | 11 (5)                    |
| Do not wish to participate in a study                   | 4 (1)                     |
| Other                                                    | 25 (11)                   |

**Attrition**

Of the 6 patients who commenced MKD, 4 completed the 12-week trial period. Two patients discontinued the diet before week 12, 1 (anaplastic astrocytoma) due to clinical deterioration leading to hospital admission, where the MKD was unsustainable and 1 patient (glioblastoma) due to dietary preferences. Median dietary duration for those discontinuing diet was 34 (22–45) days. One patient temporarily discontinued the MKD for 3 weeks during the 12-week trial period due to an unrelated chest infection, following which the diet was reinstated. Of the 4 patients who completed the 12-week trial period, 3 stayed on the diet for the longer term \((\geq 360\) days), whilst 1 discontinued the diet after 167 days due to tumor progression and clinical deterioration.

**Dietary Tolerance**

Two patients reported constipation whilst following MKD. Constipation was reported in the first 2 weeks after commencing the diet and resolved with dietary modification in all patients. No other dietary intolerances were reported by patients, such as diarrhea, nausea, vomiting, or acid reflux.

**Ketosis**

Adequate urinary ketosis of 4 mmol/l was achieved in all patients, within one week of commencing the diet. Of those who completed 12 weeks of diet \((n = 4)\), 3 maintained ketosis during this time. One patient temporarily discontinued the MKD for 3 weeks, as stated above, and therefore did not maintain ketosis during this time.

**Anthropometry**

Table 3 illustrates anthropometry (body composition) at baseline and at follow-up, after completing 12 weeks of
MKD ($n = 4$). No significant differences were noted between measures pre- and post-diet.

**Laboratory Values**

Changes in laboratory values are illustrated in Table 4 for patients with baseline and 12-week follow-up data ($n = 4$). No derangements were noted in renal, bone, or liver function biochemistry results.

**Exit Questionnaire**

Six patients completed an exit questionnaire to assess their experience of the diet and service provided. Five patients reported their weekly grocery shop had increased in cost since commencing MKD, mainly due to the added expense of high-protein foods, such as meat and fish, fats such as olive oil, and specialist carbohydrate free food products. All patients would recommend the MKD and all patients would recommend the WCFT ketogenic service to other patients. The majority of patients ($n = 4$) would recommend commencing the diet after surgery, before radiotherapy, from their experiences. Four patients expressed an interest in participating in a clinic trial to assess effectiveness and tolerability, of which 1 patient would still be interested if the trial were randomized.

Cost Analysis

Costs of the initial 12-week intervention can be found in Table 5. These costs were based on the dietetic intervention equating to 8.8 h per patient (4 nonclinical, 4.8 clinical) over a 12-week period. Biochemistry and ketone monitoring were calculated based on timings and tests stated in the methodology above.

**Discussion**

The results of this service evaluation provide evidence for the feasibility of a ketogenic service for adults with glioblastoma, within the NHS.

The questionnaire data indicate that there would be sufficient patient interest to support a clinical trial. However, patient participation in a clinical trial would be affected by randomization if the control arm was standard treatment with no KD. However, the James Lind Alliance Neuro-Oncology Priority Setting Partnership report identified that the influence of lifestyle factors (including diet) on tumor growth was one of the top 10 clinical uncertainties. Since the most effective way to assess dietary influence and therefore effectiveness would be to undertake a RCT, careful consideration of the trial design would be needed to ensure maximum recruitment, whilst achieving maximum methodological integrity. Nevertheless, our patient survey results should be interpreted with caution due to reporting bias, since those interested in KDs are more likely to seek out information online.

### Table 2. Baseline demographics.

| Patient | Gender | Age | Histological diagnosis$^3$ | Treatment during diet | Prior treatment | Dexamethasone dose (mg/d) during diet |
|---------|--------|-----|---------------------------|----------------------|----------------|----------------------------------|
| 1       | Male   | 34  | Glioblastoma IDH1 wildtype| CCNU                 | Sx, RT, TMZ     | 0–1$^*$                          |
| 2       | Male   | 47  | Glioblastoma IDH1 wildtype| RT, TMZ              | Sx              | 2–6$^*$                          |
| 3       | Male   | 66  | Anaplastic astrocytoma IDH1 wide-type| RT, TMZ | Sx              | 0                               |
| 4       | Male   | 44  | Glioblastoma IDH1 mutant | TMZ                  | Sx, RT, Sx, Gliwafers | 0–12$^3$                       |
| 5       | Male   | 45  | Glioblastoma IDH1 wildtype| TMZ                  | Sx, RT         | 0.5–1$^*$                        |
| 6       | Male   | 49  | Glioblastoma IDH1 wildtype| RT, TMZ              | Sx              | 2                               |

Abbreviations: CCNU, Lomustine. IDH1, isocitrate dehydrogenase 1. RT, radiotherapy. TMZ, temozolomide. Sx, surgical resection. Bx, biopsy. Histology classified by WHO 2007 criteria in use at time of diagnosis (20).

$^*$Dexamethasone dose decreased whilst on diet.

$^1$Dexamethasone dose increased whilst on diet.

### Table 3. Anthropometry changes.$^1$

|                | Baseline | 12-week review | $P$ value$^2$ |
|----------------|----------|----------------|--------------|
| Weight (kg)    | 85.6 (11.7) | 84.6 (9.6)     | 0.71         |
| BMI (kg/m$^2$) | 25.2 (23–29.6) | 25.1 (23.4–28.4) | 0.759        |
| Mid arm muscle circumference (cm) | 25.9 (22.1–32) | 30.2 (26.7–31) | 0.176        |
| Fat mass (%)   | 22.0 (11.2–25.6) | 23.0 (12.2–23.9) | 0.670        |

$^1$Paired values were available in 4 patients for all measurements.

$^2$Two sample paired t-test. Values are median (range) except weight illustrated as mean (standard deviation).

### Table 4. Laboratory values.$^1$

|                | Baseline | 12-week review | $P$ value |
|----------------|----------|----------------|-----------|
| Total cholesterol | 5 (3.6–6.2) | 7.4 (4.4–8.3) | 0.127     |
| LDL             | 2.9 (2.1–4)   | 4.7 (2.3–6.2) | 0.098     |
| HDL             | 1.8 (0.8–2.2) | 1.4 (1.4–2.6) | 0.189     |
| TG              | 0.94 (0.5–2.9) | 1.3 (0.9–1.6) | 0.863     |
| Cholesterol: HDL | 3 (3–5)       | 3.8 (3.1–5.9) | 0.153     |

$^1$Values are median (range).

$^2$Two sample paired t-test. Abbreviations: LDL, Low Density Lipoprotein. HDL, High Density Lipoprotein. TG, Triglycerides.
Table 5. Cost analysis.

| Item                              | Cost per patient for 12 weeks (£) |
|-----------------------------------|-----------------------------------|
| Dietitian (mid-point band 6 salary) | 148.50*                           |
| Biochemistry monitoring           | 108.69*                           |
| Urinary ketone monitoring         | 11.20                             |
| Administration support            | 17.61*                            |
| Total                             | 286.00                            |

*Dietetic intervention equated to 8.8 h per patient (4 nonclinical, 4.8 clinical) over a 12-week period.
*Carnitine accounts for £52.26 of total biochemistry costs. All costings are based on patients who completed the full 12 weeks (n = 4).
*Administration support equated to 2 h per patient over a 12-week period.

and via charities, resulting in a positive bias in our questionnaire data.

The key motivators for participation in KD clinical trials were distributed between helping others, improving quality of life, having access to the diet, and gaining expert advice, which should be considered in future trial designs or service models. The main barriers to participating in a KD trial include burden of dietetic visits and extra expense of travel. Burden of dietetic consultations can be addressed using the proposed service design since telephone consultations negate the expense of travel, the inconvenience of clinic attendance, and require less dietetic time. Dietitians should consider cost implications when devising diets, since our feasibility patients reported an increase in the weekly grocery shop whilst on diet. This could be addressed by the prescription of ketogenic dietary supplements; however, this would increase the cost burden to the NHS, an aspect worthy of further investigation.

Of the 8 patients referred into the service 6 were started on diet. Two patients, 1 a newly diagnosed glioblastoma post resection, the other a recurrent glioblastoma receiving second line chemotherapy, were not able to attend the first clinic appointment due to rapid disease progression and poor performance status. This highlights the challenges of starting the diet in a timely manner and it would be beneficial for future service designs and clinical trials to consider performance status as part of the eligibility criteria. The WCFT has a catchment population of approximately 3.5 million and treats around 100 to 120 newly diagnosed glioblastoma patients per year. After setting up the KD service we received 1 referral per month which represents only 10% of all new glioblastoma patients. The low referral rate is likely to be due to a combination of factors, including a lack of awareness by referring clinicians as well as a lack of suitable patients. The expected referral rates and patient demand should be considered when setting up a new KD service.

In our clinic, 4 patients completed the initial 12 weeks of diet and our attrition rates are comparable to the literature (14,21). However, it is important to note the higher carbohydrate intake of 60 g/day in the ERGO study (14), which is likely to improve dietary tolerance and compliance. Of those who completed the initial 12 weeks (n = 4), 3 stayed on the diet for the longer term, which highlights the tolerability of the diet and the motivation of the patients with a terminal tumor.

Side effects were limited, with only two patients reporting constipation which was resolved through dietary changes (the inclusion of daily linseeds/flaxseeds and increased oral fluids). No other side effects were reported by patients, including diarrhea, nausea, vomiting, or acid reflux, comparing favorably to a previous study of KD in cancer patients (14) and was below that reported in MKD epilepsy populations (16,22–24). Whether this is as a result of reporter bias or perhaps due to patient perception of acceptable gastrointestinal side effects requires further investigation. There were no clinically relevant changes in cholesterol profiles (total cholesterol, LDL, HDL, TG) over the course of the diet, contradicting previous literature (16,25). Longitudinal data, of larger populations, may provide a more informative result. The lack of reported side effects in our limited number of patients provides reassurance that the diet is safe in the glioma population. In addition, there was a median increase of 5.4 cm in mid arm muscle circumference over 12 weeks, which suggests that the MKD may not be detrimental to the nutritional status of glioma patients. This is further supported by the minimal change to weight, BMI, and fat mass, over the 12-week period. The increase in muscle could be as a result of the athletic and gender bias of our population, rather than simply diet, with 6 participating in weight-bearing exercise, 5 of whom maintained a daily aerobic exercise regime. However, future studies are required to investigate this effect in a larger population.

Adequate urinary ketosis is deemed to be ≥4 mmol/l (16), and was achieved in all patients. Stable ketosis was achieved in 3 patients who completed the 12-week dietary period. Urinary ketones were the measurement of choice, due to cost implications associated with blood ketone monitoring (£0.09 per urinary ketone strip versus £2.50 per blood ketone strip). We acknowledge this as a potential methodological limitation due to effects of hydration and time lag on readings, however laboratory or home testing proved too costly for implementation in this service. Urinary ketones are also limited to measuring acetoacetate and changes in the ratio of acetoacetate to beta-hydroxybutyrate, may result in low readings, as the patient becomes keto-adapted. In future trials, blood ketones may be considered, but the implications of monitoring should be considered within NHS economic models and frameworks.
Dietetic involvement per patient over 3 months was 8.5 h (4 h nonclinical, 4.8 h clinical) ensuring a viable NHS service model, costing £286 per patient for 12 weeks. In previous KD trials in paediatric epilepsy (15,17) and for commissioned paediatric epilepsy KD services patients are screened for carnitine deficiencies and fatty acid oxidation defects. We also undertook carnitine testing in our pilot, but all tests were negative, given that fatty acid disorders are rare in adults (26) and the MKD allowing free protein (source of carnitine) carnitine testing is not necessary in future adult glioma trials or KD services.

Our patients were following the diet at various stages of treatment (Table 2) which provides information on how the diet is tolerated during all parts of the patient pathway. The 2 patients who discontinued diet before week 12 were following a MKD whilst receiving adjuvant chemo radiotherapy. Whilst the literature cites this to perhaps be the most opportune time in relation to efficacy (7,8), compatibility with the side effects of the medical treatments need to be considered. Despite this, 4 of the patients who completed an exit questionnaire would recommend consuming a MKD whilst receiving adjuvant chemo radiotherapy. Future trials should assess the tolerability of MKD at this timepoint.

Our study had several limitations. The small patient numbers, predominantly well-motivated males participating in aerobic and anaerobic exercise, who all started MKD at different time-points in their treatment pathway limit interpretation of our results in the context of the glioblastoma population as a whole. Nevertheless, our study shows that the MKD can be deliverable within the NHS setting at a modest cost to the health service. Since the study was not designed to assess effectiveness, the impact of MKD on tumor control could not be assessed, and whilst all patients self-reported good quality of life, this was similarly not objectively assessed.

Conclusion

The ketogenic diet appears to be gathering momentum as an adjuvant therapy within the glioma patient population. We have shown MKD for adults with gliomas to be deliverable within a dietetic-led, NHS service. The diet itself was tolerable, with limited side effects and there appears to be high levels of interest within the glioma patient community to ensure adequate recruitment would be possible within the context of a clinical trial. Whether MKD is an effective adjuvant therapy for glioma tumors remains to be proven. Further studies are required to demonstrate patient benefit before the MKD is offered as a clinical service within the NHS.

Location

This work was carried out at The Walton Centre NHS Foundation Trust, Liverpool, UK and The University of Liverpool, Liverpool UK.

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