**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 increasing interest in the use of the ketogenic diet (KD) as an adjuvant therapy for glioma patients. We assessed the tolerability and feasibility of the modified ketogenic diet (MKD) in patients with glioma, along with willingness of patients to participate in a future randomised controlled trials. The study was undertaken in two parts; a patient questionnaire and evaluation of the diet.

172 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 or 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.

**Key words**

Ketogenic, diet, adult, glioma.

**Introduction**

Gliomas are the commonest primary malignant brain tumour in adults. Despite current treatment for high grade gliomas, such as anaplastic astrocytomas and glioblastomas, includingmaximal surgical resection, radiotherapy and temozolomide chemotherapy, the overall survival remains poor, with 27% of glioblastomas surviving beyond 2 yearsand 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]) has not improved the survival for patients with these tumours. Therefore, alternative treatment options are being explored. There is increasing interest in using the ketogenic diet (KD) 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 tumours 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 reduced peritumoural oedema [9]. Whilst showing promising anti-tumour effects in animal models, effectiveness in humans has yet to be established through survival data.

Recent studies investigating the use of the ketogenic diet 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 tumour patients. There are few existing services in place to support a randomised 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 may be the most suitable for adults undergoing oncological treatments. There is no need for a fasting start or hospitalisation 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, diarrhoea 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 randomized controlled trial.

**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 patient’s baseline demographics, attitudes towards 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 tumour charities websites (Matthew’s Friends, Astro Brain Tumour Fund, The Brain Tumour Charity, brainstrust) 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) ≤18.5kg/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 analysed. Telephone reviews were utilised for trouble-shooting 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 20g/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 ≥4mmol/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 summarise 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

172 questionnaires were completed – 50 at WCFT clinics and 122 online. Fourty percent (n=69) of participants were male, 51% (n=88) female, 9% (n=15) not recorded, all aged between 16-69 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 report 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 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 randomised 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.

*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 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 (≥360 days), whilst 1 discontinued the diet after 167 days due to tumour progression and clinical deterioration.

*Dietary tolerance*

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

*Ketosis*

Adequate urinary ketosis of 4mmol/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, 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 randomised into MKD with standard care and standard care alone. All patients would consider following the diet for longer than 12 weeks as part of a clinical trial.

*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 hours per patient (4 non clinical, 4.8 clinical) over a 12 week period. Biochemistry and ketone monitoring were calculated based on timings and tests stated in 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 randomisation 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 tumour 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 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 60g/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 tumour.

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 diarrhoea, 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 5.4cm 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 who 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 ≥4mmol/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 hours (4 hours non clinical, 4.8 hours 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 delivered 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 tumour 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 tumours remains to be proven. Further studies are required to demonstrate patient benefit before the MKD is offered as a clinical service within the NHS.

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brainstrust

Matthew’s Friends

The Brain Tumour Charity

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**Conflict of interest**

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