**The modified ketogenic diet for adults with refractory epilepsy: an evaluation of a set up service**

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**Abstract**

Purpose: The ketogenic diet (KD) has been proven to be effective in children with refractory epilepsy and is recommended by the National Institute of Health and Care Excellence (NICE). There is no randomised control trial (RCT) evidence for the clinical or cost effectiveness of KD in adults, for whom the KD is not currently recommended. We assessed the feasibility of the modified ketogenic diet (MKD) in adults with refractory epilepsy along with the willingness of patients to participate in a future RCT. Methods: The service evaluation was undertaken in two parts; questionnaire and diet evaluation. Results: 102 patients completed a questionnaire, of which 51 patients were willing to try the MKD for 3 months to assess effect on seizures. Forty three patients were willing to participate in a clinical trial to investigate deliverability, efficacy and tolerability. Thirty seven of which would still be willing to participate if the trial were randomised. Of the 17 patients who commenced the diet, 9 completed the 12 week period, 7 of which stayed on the diet for the longer term. Constipation (n=6) and loose stools (n=3) were the only reported adverse effects. Conclusion: Our results indicate that there is demand for a ketogenic diet service in adults. The MKD is well tolerated, feasible and financially viable to deliver to adults with epilepsy in the NHS. There is also interest in and willingness to participate in a UK based RCT that would ultimately inform decisions about commissioning appropriate services.

**Highlights**

* Modified ketogenic diet therapy is feasible within an NHS setting, for adults with epilepsy.
* The diet is tolerable, with limited side effects.
* A large scale trial is required to investigate the efficacy of MKD.
* This population is interested in participating in MKD trials to assess efficacy.

**Key words**

Ketogenic, diet, adult, epilepsy. [[1]](#footnote-1)

**Introduction**

The ketogenic diet (KD) has been proven to be effective in children with refractory epilepsy and is recommended as a treatment option by the National Institute of Health and Care Excellence (NICE) [1]. However, there is no randomised control trial (RCT) evidence for the clinical or cost effectiveness of KD in adults [2]. As a result, the KD is not routinely recommended as an NHS treatment for adults with treatment refractory epilepsy in the UK, nor is it recommended in other EU countries.

The majority of new AEDs have been developed based on knowledge of neuron excitability and through mass screening of drugs in animal models. Whilst more than 20 new antiepileptic drugs (AEDs) have been developed over the past 30-40 years, there has been no substantial decrease in the proportion of patients with uncontrolled seizures. Given this failure, it is important to assess other treatment options such as the KD. However, designing and delivering a KD service, and assessing is clinical and cost effectiveness pose a number of challenges that need to be considered and addressed.

One challenge is access to a service that can provide the KD for both patients in a trial and as an NHS treatment. The arguments here can be somewhat circular, as at present few services are commissioned to provide the KD for adults. As a result there are few services in place to support a RCT, but commissioners will not commission further services without good evidence of cost effectiveness. We therefore need evidence about feasibility, service throughput and costs to design the most efficient means of delivering the KD to adults with refractory epilepsy in the NHS.

A second challenge is to choose the most appropriate type of KD to provide. There are various types of KD, including the classical KD (4:1 ratio of fat to carbohydrate and protein, ~90% fat), the medium chain triglyceride (MCT) KD (~75% fat), the modified ketogenic diet (MKD, ~80% fat) and the modified Atkins diet (MAD, ~65% fat). There is a trend within RCT evidence for KDs with a higher fat and lower carbohydrate content to have greater antiepileptic efficacy [2]. However, these KDs are also associated with a greater number of side effects.

The MKD is the least restrictive KD and induces ketosis through encouraging a high fat and low carbohydrate intake, but without the requirement to limit protein, fluid or energy intakes, in contrast to other KDs. There is no need for a fasting start or hospitalisation to commence the diet [3], promoting ease of use and reducing costs. As with all KDs the MKD has some side effects, however these are predominantly gastrointestinal related (constipation, diarrhoea and reflux), along with raised lipid profiles and weight loss. In an adult population this weight loss may be a desirable outcome in those overweight and obese individuals [4]. On balance the MKD is the intervention that is most likely to be tolerated by adults with refractory epilepsy and the diet we have chosen to assess.

This study has two parts. Firstly, we assessed patients’ views about access to a KD service and their willingness to participate in an RCT. Secondly we assessed the feasibility of delivering a KD service in a unit with no prior service.

**Materials and Methods**

Questionnaire development was undertaken by a multi-disciplinary team, including a Neurologist, Neurosurgeon, Biostatistician and Dietitian at the University of Liverpool and The Walton Centre NHS Foundation Trust (WCFT). Data collected included demographics, attitudes towards the use of the MKD in refractory epilepsy, willingness to try the diet and willingness to participate in a RCT. The questionnaire contained background information regarding the MKD to assist patients in making an informed decision. The questionnaire was circulated to patients attending WCFT Mersey region, epilepsy clinics.

Patients attending these clinics were offered the opportunity to try the MKD for a 3 month period. Ketogenic service inclusion criteria included age ≥18 years, patient at WCFT, prior use of at least 2 anticonvulsant medications, at least 2 seizures per month. Exclusion criteria included having prior use of a KD, kidney dysfunction (chronic kidney disease, renal stones, cancer, low phosphate/ potassium/ salt diets), liver dysfunction (alcoholic liver disease, non-alcoholic liver disease, cancer, hepatitis, haemochromatosis, primary biliary cirrhosis), gall bladder dysfunction (gall stones, cholecystectomy in past 12 months, cancer), metabolic disorder (carnitine deficiencies, β oxidation defects [medium-chain acyl-CoA dehydrogenase deficiency, long-chain acyl-CoA dehydrogenase deficiency, short-chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl CoA deficiency, medium chain 3-hydroxyacyl CoA deficiency], pyruvate carboxylase deficiency, porphyria), eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder), diabetes (requiring medication), body mass index (BMI) ≤18.5kg/m2 and current use of weight loss medications (Orlistat, Belviq, Contrave, Saxenda, Phentermine and Qsymia).

Patients were encouraged to consume dietary fat to 70% of total energy and dietary carbohydrate was limited to 20g/day (3-5% total energy requirements), both of which were calculated using portion lists. Protein sources were not restricted. All patients commenced the diet at home, without a fasting start. The schedule of clinical assessments and appointments are illustrated in figure 1. Seizure type and frequency were documented at baseline. Nutritional analysis of food diaries was undertaken using DietPlan 7© (Forestfield Software LTD, Horsham, UK). Dietary adherence and tolerance were monitored, along with changes to medications. Medications were altered according to Consultant Neurologist recommendations.

*Figure 1: Schematic of service design*

Appointment booked by telephone and KD information sheet posted

**Clinic appointment 1 (45min)**

Baseline assessment (A B C)

**Clinic appointment 2 (1hr)**

Education and commence MKD

**Group appointment 2 (1.5hrs)**

Education and commence MKD

**Telephone review 1** (week 1)

**Telephone review 2** (week 3)

**Clinic appointment 3 (45min)**

A B C (week 6)

**Telephone review 3** (week 9)

**Clinic appointment 4** **(45min)**

A B C D (week 12)

|  |  |
| --- | --- |
| Key | |
| A | Anthropometry (weight, height, BMI, MAC, TSF, MAMC, FM) |
| B | Biochemistry (renal, bone, LFT, fasting lipid, fasting glucose, carnitine [only on initial screen]) |
| C | Collect food and ketone diaries |
| D | Service evaluation questionnaire |

BMI (Body Mass Index), MAC (Mid Arm Circumference), TSF (Tricep Skin Fold), MAMC (Mid Arm Muscle Circumference), FM (Fat Mass), LFT (Liver Function Test) Patients were provided with hospital literature regarding MKD, recipes, ketostix® (Bayer, Leverkusen, Germany), ketone diaries and a personalised 7 day MKD diet plan calculated by the dietitian, when commencing the diet. Patients were also instructed to check their urinary ketones twice daily (morning pre breakfast and 2 hours postprandial of an evening) for the first month, once per day for the second month, then twice weekly in the third month of diet. Figures were recorded in the ketone diary provided. Adequate urinary ketosis was defined as 4mmol/L [4]. For those patients with a BMI≥25kg/m2 who wished to lose weight, a weight loss of 0.5-1kg/week was encouraged, aiming for a total weight loss of 5-10% over the 12 week duration of the diet. At week 12, or upon exit from service if prior to this, patients were requested to complete a questionnaire to assess dietary tolerance, feasibility, willingness to participate in future RCTs, longitudinal studies 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. The service evaluation was approved by WCFT Research, Development and Innovation committee.

**Results**

Questionnaire results

One hundred and two questionnaires were completed. Forty seven of the respondents were male and 55 female. Thirty nine were aged 18-29 years, 35 aged 30-49 years and 26 aged 50+. Seventy eight reported experiencing 3 or more seizures in the previous 2 months.

Fifty responded that the MKD should be offered to patients with refractory epilepsy, within an NHS setting. Fifty one reported a willingness to try the MKD for 3 months. Forty three indicated that they willing to participate in a clinical trial to investigate deliverability, efficacy and tolerability, whilst 37 would still be willing to participate if the trial were randomised.

Patients were also questioned about their motivators and barriers to participating in a clinical trial. The results of which are illustrated in table 1.

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| --- | --- | --- |
| Table 1: Motivators and barriers identified to participating in a clinical study | | |
| Motivating factors |  | **Number of responders** |
| To help other adults with epilepsy | | 55 |
| To access the diet myself | | 34 |
| To get expert advice about the diet and my epilepsy | | 46 |
| To improve seizure control | | 63 |
| To improve quality of life | | 52 |
| Other | | 7 |
| Barriers to participation | |  |
| Extra burden on visiting a dietitian | | 29 |
| Not enough time to devote to the study | | 29 |
| Extra expense of travelling | | 27 |
| Extra expense of the diet | | 30 |
| Do not wish to participate in a study | | 13 |
| Other | | 9 |

Feasibility and tolerability of the MKD

Forty five patients were referred to the dietitian for consideration of MKD, 17 of which commenced diet. Table 2 illustrates the flow of adults through the service.

|  |  |
| --- | --- |
| Table 2: Flow of adults through the service | |
| Referral figures | **Number of responders** |
| Referred to dietitian | 45 |
| Commenced diet | 17 |
| Patient decline intervention | 15 |
| MKD contraindicated | 9 |
| Did not attend first appointment | 4 |
| Reasons for declining dietary intervention |  |
| Baseline bloods not undertaken by patient | 2 |
| MKD unacceptable to patient | 9 |
| Unable to provide hospital transport | 1 |
| Increased number of clinic appointments | 2 |
| No response to invitation letter or telephone call | 1 |
| Unable to complete 12 week trial | 1 |
| Reasons MKD contraindicated |  |
| History of liver disease | 1 |
| History of kidney stones | 1 |
| BMI<18.5kg/m2 | 1 |
| Previously followed KD | 1 |
| Hypercholesterolemia with statins | 3 |
| Cholecystectomy | 1 |

Of the 17 patients commenced the MKD, 13 were female. The median age was 36 years (range 18 to 62) and median number of AEDs currently taken was 3 (range 2-4). Thirteen patients and their relatives (when appropriate) were educated on MKD at a 60 minute clinic visit and 4 patients were educated at a 90 minute group session. The same information was provided in both settings.

*Attrition*

Of the 17 patients who commenced the diet, 9 completed the 12 week period. Two patients did not commence diet following the education session, one was lost to follow up and 5 discontinued the diet. Reasons for discontinuing the MKD included dietary preferences (n=3), loose stools (n=1) and increase in seizures (n=1). Median days from dietary commencement to discontinuation for these patients were 42 (range 4-80) days. Of the 9 patients who completed the 12 week period, 7 stayed on the diet.

*Dietary tolerance*

Constipation was reported by 6 patients; this started within the first 2 weeks after initiating the diet and resolved with dietary modification in 5 patients. One patient required short term use of laxatives, but habitually suffered with constipation. Loose stools were experienced by 3 patients and resolved within the first 2 weeks of dietary initiation for 2 patients, whilst the third patient discontinued the diet at 80 days as a result. No other dietary intolerances such as nausea, vomiting or acid reflux were reported by patients.

*Ketosis*

Adequate urinary ketosis of 4mmol/L or more was achieved in 13 patients by the end of week 1 following dietary commencement and in 16 of the patients by week 3. The 1 patient who did not achieve ketosis was lost to follow up after not attending clinic appointments.

*Adherence*

Of the 9 patients who completed the feasibility period, 5 completed a food diary at week 12, from which adherence was assessed. All patients met the dietary fat target of 70% total energy (mean fat intake 74.8±4.15% of total energy/day) and 3 patients adhered to the carbohydrate target of 20g per day (mean carbohydrate intake 17.6±9.43g/day). Two patients exceeded the carbohydrate target and consumed 25.5g/day and 30g/day, but remained in ketosis (4-8mmol/l).

*Anthropometry*

Table 3 illustrates anthropometry (body composition) at baseline and at follow up, after completing 12 weeks of MKD (n=7, male n=2, female n=5). The majority of patients were overweight or obese prior to commencing the diet (n=6 of the 7 patients included in table 3; n=14 of the 17 who commenced diet). Weight, BMI, fat mass and mid arm muscle circumference all reduced whilst following the diet, however only a reduction in mid arm muscle circumference was significant (p=0.013).

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| Table 3: Anthropometric changes 1 | | | | | | | |  |
|  | **Baseline** | | | **12 week review** | | | | **P value** |
|  | **Men** | **Women** | **Combined** | **Men** | | **Women** | **Combined** | **Combined** |
| Weight (kg) | 95.5  (4.05) | 73.4  (18.2) | 79.7  (19.9) | | 86.5  (0.5) | 70.5  (14.9) | 75.0  (15.7) | 0.08 |
| BMI (kg/m2) | 30.0  (28.5-31.4) | 29.0  (23.8-41.3) | 29.0  (23.8-41.3) | 27.3  (27.1-27.4) | | 26.9  (23.9-37.8) | 27.1  (23.9-37.8) | 0.102 |
| Mid arm muscle circumference (cm) | 28.5  (26.6-31.1) | 26.6  (21.6-31.1) | 26.6  (21.6-31.1) | 29.3  (27.8-29) | | 23.5  (20.9-28.4) | 23.8  (20.9-29) | 0.013\* |
| Fat mass (%) | 31.3  (30.7-31.8) | 38.5  (30.7-48.9) | 31.3  (30.7-48.9) | 27.0  (24.9-29) | | 36.9  (27.9-45.9) | 28.5  (24.9-45.9) | 0.129 |

1Paired weight, BMI, mid arm muscle circumference were available in 7 patients. Paired fat mass values were available in 4 patients. Values are median (range) except weight illustrated as mean (standard deviation). \*indicates significant result (p<0.05), assessed using a two sample paired t-test.

*Laboratory values*

Laboratory values at baseline and 12 week follow up were available for 6 patients. There was no change in total cholesterol; base line 5.1mmol/L (4.3-7.6mmol/L) and at 12 weeks 5.1mmol/L (4.1-8.27mmol/L). There were non-significant reductions in low density lipoprotein (LDL) 3.45mmol/L (2-5mmol/L) to 3.00mmol/L (2-4.49mmol/L), high density lipoprotein (HDL) 1.82mmol/L (1.19-2.14mmol/L) to 1.67mmol/L (1.22-2.32mmol/L), triglycerides (TG) 1.1mmol/L (0.61-1.76mmol/L) to 0.9mmol/L (0.61-1.37mmol/L) and the total cholesterol: HDL ratio 3.35 (2.5-5.6) to 3 (2.5-4.2). One patient experienced low adjusted calcium after following MKD for 12 weeks. No other derangements were noted in renal, bone or liver function biochemistry results.

*Cost analysis*

Costs of the initial 12 week intervention can be found in table 4. All costings are based on patients who completed the full 12 weeks (n=9). Additional costs occurred for the initial development of the service and resources. This was completed by the dietitian over 6 weeks, full time, costing an additional £5257.

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| --- | --- | --- |
| Table 4: Cost analysis |  |  |
| Item | **1:1 Dietary Initiation** | **Group Dietary Initiation** |
| Dietitian (mid-point band 6) (£) | 116.81\* | 106.80Ɨ |
| Biochemistry monitoring (£) | 108.69× | 108.69× |
| Urinary ketone monitoring (£) | 11.20 | 11.20 |
| Administration support (mid-point band 2) (£) | 17.61# | 17.61# |
| Total cost per patient for 12 weeks | 254.31 | 244.30 |

\*Dietetic intervention equated to 7 hours per patient (3 non clinical, 4 clinical) over a 12-week period. Ɨ Providing dietary commencement as a group education session rather than a 1:1 in clinic reduced contact hours to 6.4 hours per patient, based on group size of 4. ×Carnitine accounts for £52.26 of total biochemistry costs. #Administration support equated to 2 hours per patient over a 12 week period.

**Discussion**

This service evaluation provides evidence that it is feasible to set up a ketogenic diet service providing the MKD to adults in NHS organisations with no prior service, and that such a service is not costly. However, it is unlikely that services will be commissioned for adults until there is reliable evidence regarding clinical and cost effectiveness. However, this will require future RCTs utilising such services to provide the evidence.

Results from our questionnaire indicate that adults with refractory epilepsy are interested in accessing KD services and would be willing to participate in a trial, including a RCT with a 50% chance of being allocated to the diet. Many included patients had previously taken part in clinical trials at WCFT, which may explain the positive response to participating in a trial that was randomised. Willingness to participate in a clinical trial was also greater in those patients who completed the 12 week diet trial, perhaps due to increased understanding of the diet and its impact on lifestyle.

Patient’s key motivators to clinical trial participation include improved seizure control, quality of life and helping other patients with epilepsy. Barriers to participation included burden of dietetic visits, time commitment, expense of travel and expense of the diet. Through setting out a clear service plan, patients will be able to make an informed decision prior to commencing a trial. Telephone consultations will also relieve expense of travel and potentially reduce dietetic time. It is also important to recognise that three quarters of patients on the MKD indicated an increase in the cost of the weekly grocery shop. It is unlikely that the NHS would meet such costs and dietitians should consider cost implications when devising diets.

Of the 45 patients referred into the service only 17 commenced the diet. This highlights the importance of patient selection and screening prior to referral or initial dietetic appointment, which should improve as neurologists and specialist nurses become more familiar with the intervention. Thus reducing the number of patients referred who have contraindications to the diet. It is still likely however, that a significant number of patients will decide not to proceed with the diet following consultation with the dietitian, 9 out of 45 in our sample. Of the 17 commencing the MKD, 9 were still taking the diet at 12 weeks, an attrition rate similar to other reports in adults and higher to that in children. These factors would all need to be considered in the design of any service and the design of future trials.

A further cost to consider is the biochemical screening and monitoring that is required. Testing plasma carnitine for example is expensive (costing £52.26 per test) and it is very unlikely that an adult population, in contrast to a paediatric population, will have an inborn error of metabolism, given the rare reports [5]. The MKD also provides adequate quantities of protein (a source of carnitine), therefore is unlikely to pose the risk seen in paediatric populations when commencing KDs. Screening, and hence costs, could therefore be kept to a minimum in selected adult cases.

The MKD was well tolerated, but similar to other reports [4,6–8] some patients reported loose stools or constipation, which largely resolved through dietary changes (the inclusion of daily linseeds/flaxseeds and increased oral fluids). No other side effects such as kidney stones or fatty liver were reported, however this may have been due to the short nature of the service evaluation. No significant changes were observed in cholesterol profiles (total, LDL, HDL, TG) over the course of the diet, contradicting previous literature [6,9]. However, weight loss may have been an influencing factor [10]. Longitudinal data may provide a more informative result. The lack of reported side effects could provide positive justification for the diet being safe in the adult epilepsy population.

Finally, our study demonstrates group education sessions are feasible and well received in this population, which would induce cost saving measures within an NHS setting once group capacity is maximised. The groups also provide patients with an opportunity for patient peer support.

This study has several limitations. Our questionnaire lacked validity and is subject to reporter bias. There may also be an element of researcher imposition when developing the questionnaire, through the researcher deciding what is important to patients. The questionnaire was however simple to administer and timing, resulting in an adequate number of responses. Given the questionnaire was completed in a regional epilepsy clinic; it may be appropriate to generalise the results to the wider UK epilepsy population.

With regards to feasibility methodology the small number of patients and a predominately female population may not represent the refractory epilepsy population as a whole and our practice may not be representative of other adult epilepsy centres. Our lack of a detailed study protocol may also hinder reproducibility in other centres, outside of this immediate study team. However, we have aimed to design a cost effective and obtainable service structure that can be adopted from the figures above. As this is a feasibility project and was not designed to assess efficacy, the effect of the diet on seizure control could not be assessed. Our reporting of gastrointestinal intolerances and adherence was self-reported. Food diaries are subject to reporter bias, which could reflect the positive result observed in this study regarding dietary adherence, when compared to the low completion rate. Two patients exceeded the carbohydrate target but remained in ketosis, highlighting the individuality of dietary ‘prescriptions’. Future studies should consider appropriate pre and post intervention outcome measures using validated tools. It would also be of interest to consider the impact to patient quality of life. We selected urinary ketone monitoring for this feasibility study due to the cost implications of serum ketone monitoring. However, we acknowledge this as a potential methodological limitation due to effects of hydration and time lag on readings. Future trials and services should consider the implications of monitoring within NHS economic models and frameworks. The duration of this study was suitable to assess feasibility, however long term follow up would be of interest to further assess the impact of the diet on serum lipids, anthropometry and adverse events.

**Conclusion**

MKD for adults with epilepsy is feasible within an NHS setting. The diet is tolerated, with limited side effects. There is interest in the adult epilepsy population regarding the provision of services and participating in trials to assess clinical and cost effectiveness. The service can also be delivered in a dietetic led environment, with comparable results for ketosis and attrition rates to previous literature, whilst being financially viable. A large scale trial is required to investigate the efficacy of MKD within this population.

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**Conflict of interest**

Since undertaking this work the authors have received funding from Vitaflo (International) Ltd via a PhD Studentship for KJM.

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1. Abbreviations: antiepileptic drugs (AEDs); body mass index (BMI); high density lipoprotein (HDL); ketogenic diet (KD); low density lipoprotein (LDL); medium chain triglyceride (MCT); modified ketogenic diet (MKD); National Health Service (NHS); randomised control trial (RCT); triglyceride (TG); Walton Centre NHS Foundation Trust (WCFT). [↑](#footnote-ref-1)