The brain tumour patient experience of ketogenic diet therapy

Susan Wood*, Catherine Zabilowicz

Affiliation: Matthew’s Friends Clinics, Lingfield
*Corresponding author: Susan Wood, Specialist Ketogenic Dietitian, Matthew’s Friends Clinics, Matthew’s Friends @ Young Epilepsy
St Piers Lane, Lingfield, Surrey, RH7 6PW
Tel: +44(0)1332 864812. Mob: +44(0)7813 159737
E: s.wood@mtclinics.com

ABSTRACT:

Background
Ketogenic diet therapy (KDT) is creating immense interest across the brain tumour community, but it is currently unsupported and poorly understood in standard neuro-oncology care due to a lack of clinical trial evidence endorsing safety, acceptability and therapeutic value. We report the experiences of twenty-five adult brain tumour patients on KDT for 4-51 months, with access to the services of a dietetic team specialising in KDT for epilepsy management.

Methods
A survey was conducted to gather information on reasons for pursuing KDT, the practical issues encountered and perceptions of the impact of KDT on tumour related symptoms, gastrointestinal function, weight management and psychosocial aspects of daily life.

INTRODUCTION:
Primary tumours of the brain and central nervous system (CNS) are a group of rare, heterogeneous diseases, with widely varying outcomes. However, they are the leading cause of cancer death in the under-40s, and account for the highest average years of life lost, of any tumour type1,2.

Many patients with brain tumours also have significant symptoms impairing their quality of life, including, physical problems (weakness, poor co-ordination), functional problems, seizures, fatigue, depression and cognitive impairment3. These may be due to the disease, its progression, treatment side effects, or a combination of these. In addition, uncertainty around prognosis contributes to patients’ anxieties and concerns4-5. For many patients and their families, the need to actively contribute to the management of their brain tumour with its associated physical and emotional symptoms is a powerful motivator and 32-41% of glioma patients are reported to explore complementary therapies and consider lifestyle change to manage symptoms and prolong survival6.

The low carbohydrate, high fat, adequate protein ketogenic

Results
Twenty-five patients (71%), aged 30-71 years (median 46 years), on KDT for 4-51 months (median 11 months) completed and returned the survey. Nineteen (76%) had sustained KDT through episodes of surgery, chemotherapy, radiotherapy or combinations of these. All eight patients (100%) experiencing regular seizures and eleven of fourteen (79%) with fatigue reported improvements in these symptoms. Twenty patients (80%) reported weight-loss, particularly in the early weeks; for thirteen (65%), this was a positive side-effect. The most common adverse effect was constipation, reported by ten patients (40%). In both symptomatic and asymptomatic brain tumour patients, support for their choice to pursue KDT was readily reported to underpin their sense of empowerment and control.

Conclusions
Notwithstanding that the primary reasons for over 50% of the patients to commence KDT was to prolong survival, this study is unable to make any observations in this area. However, the patient experience would appear to show that refractory seizures and chronic fatigue may be alleviated by KDT. Furthermore, amongst the group, the survey shows KDT to be sustainable and tolerable. It would appear that KDT is worthy of further clinical exploration for its symptom management benefits alone.

Key words: Brain tumours, ketogenic diet, seizures, fatigue, quality of life.
diet (KD) is a dietary approach creating significant interest in the brain tumour community. Used for almost a century as an effective therapy for medically refractory epilepsy, KDT is known to deliver its effect by triggering a cascade of adaptations in cellular metabolism; restricting glycolysis, increasing fatty acid oxidation, increasing ketone synthesis and leading to enhanced mitochondrial respiration. It is this broad-spectrum effect leading to improved cellular fuelling that has led to increased interest in the potential of KDT to deliver neuroprotective and therapeutic benefits to a wider range of neurological conditions beyond epilepsy.

Research conducted by Otto Warburg in the 1920's led to his proposal that tumour cells typically display a shift in metabolism characterised by an increased reliance on glycolysis even in the presence of oxygen; a fundamental difference from the metabolic characteristics of healthy cells of the same origin. Now widely recognised as a hallmark of cancer, the Warburg effect provides a rationale for the exploration of the KD as a strategy to selectively disadvantage brain tumour cells by altering the biochemical climate in which they reside. Preclinical studies of KD in glioma models indicate that ketosis mediates its impact by reducing glucose and insulin levels, modulating oxidative stress, reducing inflammation, enhancing anti-tumour immunity, altering gene expression and sensitising tumours to chemo-radiation.

Published case reports and case series of GBM and Anaplastic Astrocytoma on KD indicate tolerability, safety and direct tumour effects in some. However molecular studies and controlled trials are needed to understand whether adjuvant KD may improve progression free survival and if so, when and for how long this should be applied.

In the meantime, the potential of KDT to impact on brain tumour associated symptoms and enhance the quality of life of those living with both low and high grade tumours, has largely gone unnoticed. Decades of use of KD in cases of medically refractory epilepsy and the clinical knowledge accompanying this suggests that the positive effects on seizure management, fatigue, mental clarity and weight control may translate to brain tumour cases of all grades struggling to cope with similar life impairing symptoms. Clinical data relating to the use of the Modified Atkins Diet in eight brain tumour patients, including four with low grade glioma, with resultant seizure disorders reported a 50% seizure reduction in five of the cases.

In the UK, NHS based KD services for adults with epilepsy remain limited, with no provision for adults with brain tumours. Between 2011 and 2018, Matthew's Friends KDT Clinic, supported by Astro Brain Tumour Fund, provided charitably funded dietetic support to over 100 self-selected adults from across the UK and Ireland, who requested information and guidance to explore KD as a component of their brain tumour management alongside standard oncology care. A modified ketogenic diet (MKD); low in carbohydrate (measured), high in fat (portion guided) and moderate in protein, was used as a practical, adjustable KDT approach and individualised on a per-patient basis, with the aim of:

1. improving brain tumour related symptoms (e.g. seizures and fatigue) and overall sense of wellbeing.
2. establishing ketosis (ideally >1mmol/l) and stable glucose levels (ideally <5mmol/l) as determined by home blood monitoring.
3. supporting the individual to safely explore their choice of KDT, building confidence and self-control throughout.

The survey was conducted to evaluate the experience of KDT in these patients.
KDT information booklet

All adult brain tumour enquirers were sent an introductory booklet via email and invited to get back in touch to arrange a preliminary discussion by telephone if they wished further information/support beyond.

Pre-KDT discussions (telephone)

- Brain tumour history and treatment. Any other medical conditions and treatment. Contra-indications/cautions.
- Practical issues (dietary changes, home-monitoring requirements, importance of family/friend support), commonly reported side effects (lethargy during initial week of transition, constipation, weight loss) and commonly reported benefits (reduced fatigue, improved seizure control, weight loss).
- Medical forms and food diary completion.

KDT education session (face to face)

- MKD prescription equating to an energy distribution of approximately 5% carbohydrate, 80% fats and 15% protein based on patient’s food diary, Body Mass Index, activity levels, estimated energy requirements and whether weight maintenance or loss was desired.
- Food sources of protein CHO and fat. How to count carbohydrate and consume adequate fats using kg Carbohydrate and 10g Fat Choice Lists as a guide.
- Practical menu guidance based on food preferences and lifestyle.
- Guidance on home monitoring: weekly weight, daily blood ketone (1.0-5.0mmol/l) and blood glucose testing or urine ketone testing, symptom monitoring.
- Guidance on vitamin and mineral supplementation; for most, a one-a-day adult multivitamin and mineral, plus additional calcium, magnesium and vitamin D.

Follow up (telephone)

- Weekly contact by phone for 6-12 weeks to discuss adjustments of MKD prescription as required, based on weight, blood or urine ketones, symptom change and how they were coping with their dietary change. Throughout the KDT period, prompt response to queries by email and ongoing phone contact was available as required.
- Generally, by three months patients were becoming familiar with their new way of eating, feeling some benefits and gaining confidence and a sense of control from their efforts. However, if by three months on KDT, patients were not experiencing any benefits or finding the ‘cons’ outweighed the ‘pros’, they were encouraged to return to a mainstream low glycaemic load regime.

In the initial weeks of familiarising themselves with portion control, they were encouraged to weigh their carbohydrate choices on gram scales, while fats were more loosely portion guided to match energy requirements and prevent excessive weight loss. Protein foods were not restricted at the outset but the need for only moderate portions was emphasised. Menu guidance and planning sheets encouraged a simple, systematic approach to building ketogenic meals and a starter recipe book was provided. They were encouraged to keep meals and snacks to simple combinations initially, establishing their own personal repertoire of favoured recipes over time.

**Table 1: Stages of KDT support for adults with brain tumours.**

KDT. In two of these, it was reported to be ‘mild’ and in one, coinciding with chemotherapy only. One patient had constipation prior to starting their diet which persisted throughout and one other experienced both constipation and occasional diarrhoea on KDT. Thirteen patients (52%) reported no adverse effects of KDT on their gastrointestinal function while two (8%) reported a past-history of chronic gastro-oesophageal reflux that resolved completely on KDT.

**How did KDT affect body weight?**

Twenty patients (80%) reported losing weight on KDT, mainly in the early weeks while three (12%) gained weight and two (8%) reported no change. Most patients felt positive about the weight loss (n=13, 65%) while some felt negative (n=3, 15%) and others felt indifferent (n=4, 20%). Similarly, in those that gained weight, most felt positive about reaching their preferred level (n=2, 66%).

**How useful was it to be able to monitor blood glucose and/or blood ketone levels?**

Although twenty-one (84%) of patients found home monitoring of blood glucose and blood ketone levels useful, the majority reported feeling anxious if levels were not as hoped (n=13, 52%), particularly in the early days of KDT. One patient reported finding blood monitoring unhelpful, citing its lack of correlation with seizure control as the reason. One chose to monitor infrequently, and two others chose not to monitor their blood ketone or glucose levels.

**DISCUSSION:**

All patients with primary brain tumours face an uncertain prognosis and many experience neurological symptoms, refractory to medical management too. In this context, the desire of some patients to explore novel therapies in addition to standard oncological treatment is understandable. Over recent years, KD has gained popularity within this self-determined group as more published pre-clinical data and academic reviews of the potential of KD to influence tumour metabolism have emerged\(^1\), \(^12\), \(^19\), \(^23\). However, to our knowledge, this is the first survey to examine the views and experiences of patients choosing KDT as an adjuvant option.

The cases reported in the KDT experience group were self-selected, highly motivated to take a proactive role in their disease management and actively sought guidance. The majority found the KDT difficult to implement in the early stages, yet at the time of the survey, had managed to continue it for 4-51 months, often supported by equally motivated partners and families, working together to develop their knowledge, confidence and problem-solving skills over time. Patients reported most challenge with their KDT during times of active therapy and hospital admission where control over food choice was very difficult and they became dependent on family and friends bringing in all or part of their meals to enable continuation of their KDT.

Matthew’s Friends Clinics is experienced in the use of KDT in the management of drug resistant epilepsy in adults, and familiar with patients reporting a positive impact on the quality and frequency of their seizures and reductions in fatigue when on KDT. However, the potential for KDT to deliver symptomatic benefits appears higher in this brain tumour group, with 100% of those with frequent seizures, 79% of those experiencing fatigue and at least 50% of those with headaches, vision, speech or co-ordination problems prior to KDT reporting improvements. Surprisingly, KDT was also reported to improve a range of psychosocial aspects of life, such as improving mood, concentration, memory, anxiety and the relationship to the family in patients citing these as a prior issue. The range of benefits and the frequency at
which these are reported is notable considering the prevalence of these symptoms in the brain tumour population, the negative impact these have on daily life and how resistant they can be to existing medical management strategies. Where KDT delivers tangible improvements to life quality, it also provides positive endorsement and encouragement to the patients and their families to maintain this approach. However, in both symptomatic and asymptomatic brain tumour patients, KDT was reported to deliver a sense of wellbeing, empowerment and control in a life situation where these had been lost.

A low carbohydrate, high fat ketogenic diet can often lead to weight loss if the reduction in carbohydrate intake is not accompanied by an energetically equivalent increase in fat intake. This can be a challenging shift of emphasis for many brain tumour patients, accustomed to the prevailing ‘healthy diet’ guidelines that emphasise the benefits of carbohydrate and caution on the consumption of fats. In this survey group, 80% reported some weight loss, with the majority viewing this as a positive or neutral change. All had received guidance on the relevance of tracking weight, symptom change and side effects so that adverse effects could be noted promptly and adjusted by appropriate dietary modifications.

Gastrointestinal side effects are often associated with ketogenic diets but 52% of this survey group reported no change in gastrointestinal function and 40% reported constipation that was managed by diet manipulation, laxatives or a combination of these. Two cases resolved their chronic oesophageal reflux on KDT and this in turn added to the overall positive impact of this diet choice on their quality of life.

All patients were provided with a meter to enable blood glucose and blood ketone tracking and were supported to interpret their results within the wider context of their symptoms, medical treatments and overall wellbeing. However, blood ketone levels are highly labile, being influenced by a range of variables beyond the confines of optimally adjusted KDT and self-control over food choice, such as exercise levels, stress levels, minor or major illness and use of steroid medications. In practice, the majority reported levels of 1-3 mmol/l ß-hydroxybutyrate at some point through their monitoring process, and stable glucose in the 4-5 mmol range. However, when blood levels were not as hoped, this readily led to anxiety, particularly in the early weeks of initiation.

The optimum length of time to sustain KDT is unknown and many accept that it may need to be continued indefinitely. However, we have noted that long term adherence to a KDT may be more challenging for patients caring for young children,

Table 2: Patient reported effects of KDT on their brain tumour related symptoms, weight and gastrointestinal function.

<table>
<thead>
<tr>
<th>Tumour related symptoms</th>
<th>No. of reports of a positive effect</th>
<th>No. of reports of neither a positive nor negative effect</th>
<th>No. of reports of a negative effect</th>
<th>No. of reports of newly emerging symptom on KDT</th>
<th>Total no. of reports</th>
<th>Reports noting improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>100%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>79%</td>
</tr>
<tr>
<td>Headaches</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>54%</td>
</tr>
<tr>
<td>Problems with vision</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>50%</td>
</tr>
<tr>
<td>Problems with speech</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>66%</td>
</tr>
<tr>
<td>Problems with co-ordination</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychosocial concerns</th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>67%</td>
</tr>
<tr>
<td>Memory</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>50%</td>
</tr>
<tr>
<td>Mood &amp; Irritability</td>
<td>11</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>16</td>
<td>67%</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>Relationship with their family</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>71%</td>
</tr>
<tr>
<td>Social contact with friends</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal function</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>10</td>
<td>0%</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0%</td>
</tr>
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<table>
<thead>
<tr>
<th>Body weight changes</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>20</td>
<td>20</td>
<td>61%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>67%</td>
</tr>
</tbody>
</table>
Improving quality of life for people living with high grade brain tumours

The Macmillan Brain Cancer Rehabilitation Team (Brain CARE) is a pilot service bringing together Macmillan Cancer Support and Hertfordshire Community NHS Trust to improve the lives of people living with high grade and aggressive brain tumours. The team includes two Allied Health Professionals (AHPs) with a specialist interest in neuro-oncology and rehabilitation plus a project support worker. Since September 2018 the team has supported patients after a diagnosis of a high grade brain tumour through to end of life care - a seamless patient pathway.

A high grade brain tumour diagnosis is devastating to patients and their families with low five year survival rates. The neurological impairments impact on participation, activity and well-being. Carer burden is also extremely high. The Macmillan Brain CARE Team is building on a two year Macmillan scoping project. This mapped the pathway for people living with brain tumours and highlighted; a complex pathway spanning organisational and geographical boundaries; poor access to rehabilitation with patients falling through systemic gaps; inconsistent communication between treating teams and limited awareness around rehabilitation benefits for these patients.

This pilot hopes to redress the access inequalities to services for people with brain tumours. The specialist AHPs are working in training and the provision of ongoing support to enable prompt discussion of queries, monitoring data and diet adjustments as required. It is possible that easy access to expert support for both the patients and their families, enabled many to continue with KDT well beyond the point they may have reached alone.

CONCLUSION

Notwithstanding that the primary reasons for over 50% of the patients to commence KDT was to prolong survival, this study is unable to make any observations in this area. However, the patient experience would appear to show that refractory seizures and chronic fatigue may be alleviated by KDT. Furthermore, amongst the group, the survey shows KDT to be sustainable and tolerable. It would appear that KDT is worthy of further clinical exploration for its symptom management benefits alone.

REFERENCES
See online: https://bit.ly/2QdXoQ6