A General Scope of the Effectiveness of Ketogenic Diet on Children Health

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Abstract:
Ketogenic Diet (KD) as a treatment could reduce the symptoms of epilepsy as documented in many literatures and could kills in case of lack of discipline. There are three main types classic diet, the MCT, a modified Atkins diet and the LGI diet. These types showed different reduction in seizures. However, there are many side effects were documented associated with this treatment on children health in terms of growth, bone and renal stones, As well as, other common sides like Diarrhoea, vomiting, insufficient energy and constipation. Regardless of this, KD tolerated by most patients and less side effect than drugs. So, KD need more investigation in terms of side effect and for later life.

Keywords: *Epilepsy, KD, Ketogenic diet, Seizure*

1. Introduction

Children who suffer from intractable seizures need effective treatment. Drugs have proven effective in some cases of epilepsy and are essential for treating the condition. However, some types of antiepileptic drugs do not control seizures and have severe side effects. Therefore, many specialists and families increasingly seek efficacious ways of treatment with the fewest possible side effects. The KD is categorized as dietary therapy with low side effects when compared with drugs. It is based on release of ketones by metabolic manipulation which occur as a consequence of high fat intake, a suitable amount of protein for growth, and a low amount of carbohydrate (Papandreou et al., 2006). The KD has become more commonly used, and the effectiveness of KD is clearly apparent from the increasing number of centres that treat epilepsy with KD. By 2006 the number of these centres had reached 75 spread across 45 different countries (Freeman et al.,2006). The spread of these centres present opportunities to carry out comparative global studies to explore the extent to which there is a suitable range of KD for use as a dietary therapy for epileptic children from varied ethnic groups, to treat different types of epilepsy.

However, many studies have proven the effective role that KD can play in treating different epilepsy syndromes. Indeed, KD is considered as an alternative treatment for some types of epilepsy, and is considered as a second or third option for treating other cases such as IS for pediatric patients with refractory seizures who have not responded to antiepileptic drugs, especially corticosteroids and vigabatrin (Hong et al., 2010; Barclay,2010). Others new study prefer KD as a first option therapy(Rogovik and Goldman,2010).

A definitive study to determine the role of the KD as a first line therapy in treating children with IS was undertaken between 1996 and 2009. The study began by testing a traditional KD. Clinically, the 104 infants involved had IS including those with a new onset of IS. The diet evaluation was undertaken through contact with patients and families via phone, or via clinic visits. The EEG of participants was taken after three months. Some 64% had >50% of seizures improved at six months and a further 77% experienced improved seizures after one to two years.; In addition, some 38 became 37% seizure-free six months from starting the diet. Positive development was documented in

62%, of cases and a further 35% had improved in terms of their EEG result. A reduction of antiepileptic drugs was implemented in 29% of cases. The study observed adverse effects amongst 33% of cases and diminished linear growth was observed in 6% of cases. Of those more likely to show an improvement in their spasms, more than 90% were older at the onset of IS and had taken fewer antiepileptic drugs. This study concluded that two-thirds of children with IS treated with KD proved its efficacy after the failure of anticonvulsant drugs, especially corticosteroids and vigabatrin (Hong et al., 2010).

In addition, some studies have gone to some effort to ensure the ongoing efficacy and tolerability of the KD. A high profile study conducted by the Institute of Child Health and Great Ormond Street Hospital in 2008 in the United Kingdom evaluated the effectiveness of KD in controling seizures in a randomized control trial that had been conducted on 145 children from 2 to 16 years old.,The children had experienced frequent daily or weekly seizures and had not responded to two anticonvulsant drugs. In addition the participants had no prior history of KD treatment. There were 54 children in the KD group and 49 in the control group. However, some of the candidates did not complete the trial because 16 of them did not receive the intervention and the same number did not produce sufficient observable data. A further 10 were refused the treatment before the three month review, and 6 exhibited lactose intolerance.

Significantly, after three months the seizure rate decreased by 62% amongst the KD group whilst the rate of decrease in the control group was 36.9%. Moreover, some 28 epileptics in the diet group experienced seizure reduction of some 50% compared with four children in the control group. Furthermore, five epileptic children in the KD group experienced seizure reductions of some 90% compared with no reduction in the control group. Thus, there was no significant difference between symptomatic generalized or symptomatic focal syndromes in the efficacy of the KD. On the other hand, the common side effects that were documented in this study at the three-month review were a lack of energy, hunger, constipation and vomiting. In terms of the control group there were no changes in treatment. An assessment of the diet at the three month follow-up found that the KD helps to reduce intractable seizures in epileptic children noticeably (Neal et al., 2008).

A recent study at the Johns Hopkins Hospital in the United States saw on data collected by telephoning or emailing patients between 1993 and 2008. For this study, some 530 patients who had epilepsy were treated with the KD for more than a month. Children in the sample had their KD discontinued for six months or more. Only 254 patients' families responded either via phone or e-mail to with a survey and laboratory tests for serum lipid profile, liver, and kidney functions. Of these, some 101 patients completed questionnaires. Analysis revealed that 8% of patients preferred to eat foods containing high fat, while 52% had >50% seizure reduction at the time of discontinuing the diet. Similarly, 79% had experienced improved symptoms. However, some 96% of patients recommend using the KD to others. A total of 54% of the sample had started with KD before using antiepileptic drugs. The outcome of the study relied on analysis of the period at which the KD was stopped. The median duration since stopping the diet was up to six years. However, statistically there were no significant results, despite the observed improvement of the seizure reduction rate. Therefore, KD was demonstrated as a useful first line treatment for epileptics and was acknowledged as a viable treatment option for those who had stopped KD previously (Patel et al., 2010).

A study in India focused on the assessment of KD in terms of efficacy and tolerability. This study was conducted on 27 children aged between 6 months to 5 years old who had daily seizures and who had used at least three anticonvulsant drugs. However, the initiation of KD was non-fasting and starting KD gradually. The result of this study showed the proportion of epileptics who stayed on the KD at three, six and twelve months, was 88%, 55% and 36% respectively. Some 13 experienced seizures reduction of >50% while, 4 were seizure free at six months from starting the KD. At 12 months, the

proportion of patients who had seizure reduction of >50% was 37% and five children were seizure free. Adverse effects which were noted in this study included edema due to hypo-albuminaemia, constipation, weight loss and renal stones. The biochemical profile did not show significant changes over time, except that serum albumin was reduced and the spot urinary calcium-creatinine ratio was elevated. The outcome of this study was that the efficacy of KD as an alternative therapy to treat children with intractable epilepsy and was well tolerated, but should be continued only under continuous medical supervision (Sharma et al., 2009).

There are problems which any study or new therapy can face when implemented. This study clarified the point since it was conducted in the King Faisal Specialist Hospital and Research Centre in Jeddah which was considered the first such centre in the Kingdom of Saudi Arabia to have applied the KD as a therapy. One of the important studies that was conducted in Saudi Arabia over 2 years from 2002 to 2004 was an evaluation of the effectiveness of the KD and the range of acceptance of its implementation. . A total of eight children were included in this study aged between 1 and 14 years. Each had refractory epilepsy and multiple daily seizures and none responded to multiple anti-convulsive drugs. None were candidates for surgery. This study concluded that KD helped to reduce the number and dose of antiepileptic drugs. Furthermore, after six months three children had >50% seizure frequency reduction, and the intervention was found to have improved the level of alertness in four children. A further two however experienced no change in seizure frequency. One child had improved in neuro-development and in terms of seizures and alertness (Bahassan and Jan, 2006).

There is a degree of skepticism amongst some medics and scientists who do not believe in the safety of the KD when used as alternative therapy for refractory epilepsy in children. This skepticism relates in particular to the diet which contains high fat and low protein which may affect growth and the health of some children on KDs. One high profile study addrressed this skepticism by assessing the results of 14 children with refractory seizures and respiratory chain (RC) complex defects. They were treated without fasting and without receiving instructions relating to fluid intake. They were prescribed a classic KD including a 4:1 lipid to non lipid ratio. This study found KD was safe and could reduce seizures in children and found that it was effective with RC complex defects (Kang et al., 2007).

There are many treatment centres around the world that have implemented the KD. Some of these centres prefer one type of KD to other types for various reasons. For example some are infomred by the findings of studies and some are based on the excperience of medics and health care professionals. Some beleive their approach is more effective, and has more accuracy and reliability than other approaches. Nonetheless, it has been clarified in literature Neal et al(2007) that there is no significant difference between classic and medium-chain triglyceride (MCT) diet in terms of efficacy (Bahassan and Jan, 2006). Furthermore, there are several types of diet, but there are three very well-known types that are used universally such as the classic type, the MCT and the modified Atkins diet.

Neal et al (2007) has examined the role of two types of KD (classic and MCT) for a period of growth to check for any link between growth and calorie or protein intake amongst children. Growth data were collected from 75 children. The z scores for weight decreased at three, six, and 12 months respectively, while there were no changes in the z scores for height at 3 months. At 6 and 12 months however, hiehgt decreased significantly. The medium-chain triglyceride group at 3 and 6 months receorded that z scores for weight had decreased in both groups at 12 months. The outcomes for both weight and height were reduced during the period of therapy, despite in the latter stage of diet, protein was increased. However, there were no significant differences between the results of classical and medium-chain triglyceride diet in terms of weight, height, Body Mass Index BMI or in mean calorie intake up to 12 months(Neal et al., 2007).

Moreover, an important study which done by Kossoff et al (2006) was conducted at the Johns Hopkins Medical Institutions in the USA from September 2003 to May 2005 to determine the effectiveness and tolerability of a modified Atkins diet to treat refractory seizures in epileptic children. This study population comprised of 20 epileptic children aged between 3 to 18 years of age who did not respond to multiple antiepileptic drugs. In addition the population had experienced at least three convulsions per week. The children were treated with the modified Atkins diet for six months. With this type of diet there is no need to restrict fluid, calories or protein and no need to fast. However, the amount of carbohydrate needs to be limited to 10 g/day together with an increased intake of fats. Some 13 children experienced improvements in their seizures of >50%, and 7 experienced improvements of >90%. A further 4 participants became seizure free. In addition, the seizure frequency mean after 6 months was 40 seizures per week. Furthermore, serum blood urea nitrogen and cholesterol were increased to an acceptable level as a prospective result of the diet while creatinine and weight did not change and BMI remaineds stable. This study concluded that the Atkins diet is well tolerated for epileptic children and effective (Kossoff et al., 2006).

One of the innovative diets that is designed for treatment purposes is the Low Glycemic Index LGI diet. This diet helps to reduce fluctuations and to maintain a stable level of blood glucose throughout the day. The diet is considered less restrictive than other types as it allows for intake of around 40 to 60 grams of carbohydrate per day in the form of LGI foods such as whole grains (Muzykewicz et al.,2009).

A recent retrospective study was conducted at Massachusetts General Hospital in the USA (Muzykewicz et al.,2009). The study set out to investigate the efficacy, safety, and tolerability of the LGI diet to treat pediatric epilepsy. It involved participaiton from 76 children who had received the LGI diet between 2002 and 2008. The experiment set out to evaluate the efficacy and tolerability of this diet. All patient information had been collected by clinical visits, phone or email communication, and laboratory results. These data included demographic and clinical information such as seizure type, seizure frequency, medications, blood chemistry,side effects, and anthropometrics.The diet was initiated for outpatients and the dietitian instructed patients about the process and the total carbohydrate limitation of 40–60 g per day.The seizure frequency evaluation and follow up was at 1, 3, 6, 9, and 12month intervals and the efficacy of the diet was assessed by lower serum glucose levels. Eight particiupants experienced reduced seizure frequencies of more than 90% including four who became seizure free. However, three patients experienced side effects including transient lethargy and elevated Blood Urea Nitrogen (BUN). No significant changes in BMI or BMI z-score were observed. The main reason for discontinuing this diet was that the diet was restrictive, as reported by 18 patients (or 24% of the sample). Therefore, this study found that the LGI diet reduced seizure frequencies amongst epileptic children. It was therefore considered effective and, furthermore, it was considered a tolerable therapy with few side effects(Muzykewicz et al.,2009).

As with any therapy, adverse effects occurred as a result of treatment, but the KD is considered a dietary therapy associated with fewer medical complications than antiepileptic drugs or surgery (Parrish, 2006). The most common side effects resulting from KD are constipation, weight loss, acidosis, renal stones, inhibits the rate of normal growth and hypoglycemia. However, these can be treated easily in many ways. Fo example constipation can be treated by adjusting the diet to increase fluid or MCT oil intake at a suitable level to prevent diarrhoea. In addition, stool softeners or laxatives can be given. The diet can be modified to the sufficient amount of protein to achieve a suitable growth range for height, weight and BMI for children. Acidosis is lowered as a result of the diet (HCO3 of 12–18mg/dL) (Parrish,2 006).

Therefore, the families of children have to be educated to better understand the signs of acidosis, particularly at the period of acute illness and diet initiation. The intake of Carbohydrate free fluids is

an effective way to control acidosis (Bahassan and Jan, 2006). Nausea and vomiting commonly occured during the period of diet initiation or based on the ketone degree, so reducing the number of meals and replacement fluids were evidenced as effective ways to treat these complications. Hypercalciuria urine acidification and hypocitraturia could result from treatment with the KD. Such conditions are known to increase the chances of developing kidney stones. This can be resolved by giving the child adequate hydration with carbonic anhydrase inhibitors. Urine alkalization can also be prescribed to children who have a high urine calcium to creatinine ratio. As a result of diet composition, the lipid profile will be changed. Total cholesterol will be increased, also low-density lipoprotein (LDL) triglycerides and very low-density lipoprotein (VLDL) as well. Such symptoms can occur during the treatment with KD. Mild depletion of carnitine could occur without symptoms at the time of initiating the diet. Therefore carnitine supplementation was the preferred treatment (Bahassan and Jan, 2006).

As observed in the randomized controlled trial study conducted by Nealet al (2008), after three months of introducing the diet. Diarrhoea, vomiting, insufficient energy, constipation and hungry presented as symptoms and the proportions for these symptoms were respectively 13%, 24%, 24%, 33% and 22%. However, only one teenaged patient was asked to stop the diet because side effects appeared before three months. A further three patients discontinued the KD because their families were apprehensive about the diet and components and regime. A further two participants refused the diet behaviourally and the remaining patients experienced highly frequent seizures, vomiting, extreme drowsiness, diarrhoea and constipation (Cross, 2009; Neal et al., 2008). Renal stones are one of the common long-term complications of KD. A study by Cross (2009) argued that the risk of renal stones as a result of KD was significant, and clarified that children who have a high excretion of calcium will be at risk more than others. It was argued that such children will experience delayed growth, especially those who remain on the diet for longer periods (Cross, 2009).

In addition, KD as a treatment may impact the bone density which may lead to a higher long term risk of developing osteoporosis and osteomalacia. The effects on bone however are negligible when compared with the side effects of using AEDs, which directly affect the absorption of calcium and vitamin D impacting negatively on bone formation. In contrast, the serum vitamin D concentrations can improve during treatment with KD as a result of supplementation(Bergqvist et al.,2008).

A study by Bergqvist et al (2008) was conducted at the Children's Hospital of Philadelphia (CHOP). The study aimed to measure the change in the Bone Mineral Content BMC in children who were treated with the KD for fifteen months. This study recruited 25 pre-pubertal children between 1 and 14 years of age with intractble seizures. The decline occurred for both of whole-body and spine BMC whether in terms of age or height were 0.6 z/y score, 0.7 z score/y, respectively. The study concludedthat children with intractable epilepsy have poor bone health, especially nonambulatory children who have low BMI. The study suggested that treatment with KD could lead to progressive loss of BMC(Bergqvist et al.,2008).

Patel et al (2010) published an important study about the long-term effects of the KD after discontinuation for more than 6 months for children who have intractable epilepsy. Nonetheless, the adverse effects that were reported in this study were growth retardation, cardiovascular disease, increased illnesses, kidney stones and bone fractures. Some 19 families some of the symptoms that their child faced such as shortness of breath or fatigue. In two cases renal stones had developed after KD was discontinued. In terms of bone fractures, eight cases were reported after discontinuing KD, and an increase in illnesses such as infections were reported in eight cases (Patel et al., 2010).

Furthermore, a recent systematic review which was concerned with investigating these complications was based on an analysis of 27 studies which recorded the side effects that had occurred during the

process of treatment using the KD. Some events were rare, such as vomiting and raised serum lipid levels but some patients experienced more than one adverse reaction. Furthermore, there were 18 cases that were documented to have died during the diet. For 16 of these there was no sufficient demographic information to add context to the findigns. Another case suffered from pancreatitis and another had propofol infusion syndrome which is caused by impaired fatty acid oxidation, where KD are based on high amount of fat(Daniel and Keene, 2006; Baumeister et al,2004).

In addition, some experimental studies have proven memory impairment can occur in some patients with KD. Conversely, some studies contradicted these findings, and reported some development in the cognitive behavior of children, as well as some increased alertness occuring even before stopping antiepileptic drugs. However, rare side effects were documented such as pancreatitis, cardiomyopathy, vitamin D, calcium and mineral deficiency, platelet dysfunction, neutrophil dysfunction, osteoporosis, hypoproteinemia, renal tubular acidosis and basal ganglia changes (Rogovik and Goldman, 2010).

2. Conclusion

this literature review has provided some documentation of previous studies focussing on the role and effectiveness of the KD to treat children with intractable epilepsy with different types of KD diet. These include the classic diet, the MCT, a modified Atkeins diet and the LGI diet. Generally the results of these studies evidenced that KD is useful in treating epilepsy. In addition KD is tolerated by a majority of patients. Despite skepticism about the efficaciousness of the KD and despite documented side effects many studies consider the KD to have fewer side effects than antiepileptic medications.

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