Introduction

For centuries, epilepsy and its precipitating seizures have baffled caregivers while scientific communities have searched for effective treatments. Dietary manipulation, as one form of therapy for seizures, has existed since biblical times (1). During the early 1920s, a significant advancement was achieved when Wilder developed a diet having a high ratio of ketogenic foods (fats) to anti-ketogenic foods (carbohydrates and protein) (2). For several years after its introduction, the diet was widely used as a treatment for childhood seizures by mimicking the biochemical changes associated with starvation, and thus, switching the body's energy from glucose to ketone bodies. However, its popularity declined during the ensuing decades as other, more convenient antiepileptic drugs (AEDs) were developed. Despite the greater popularity of standard AEDs, the ketogenic diet never really died out, a testimony to its effectiveness in certain severe cases. In the mid 1990s, the diet enjoyed a resurgence in popularity (3, 4), and its efficacy in the modern era has been confirmed with the aid of long-term clinical studies (5-8) and animal models (9-14). This paper discusses recent scientific advancements in our understanding of the ketogenic diet with respect to seizure prevention efficacy, diet complications, cost benefit analysis, and newly proposed underlying mechanisms. Collectively, these aspects contribute to an enhanced quality of life for epileptic patients.

Ketogenic diet efficacy

Because the diet's renewed interest began several years ago, long-term and multicenter studies are now available. In the largest study to date (n=150 children), Freeman et al. reported that at one year, 50% had a greater than 50% decrease in seizure frequency and 27% were seizure-free or had a greater than 90% decrease in seizure frequency (6). In a similar multicenter study (n=51 children), at one year, 40% of those starting the diet had a greater than 50% decrease in seizures, and 10% were completely free of seizures at 1 year (5). Finally in the longest study to date, Thompson et al. followed 54 patients on the ketogenic diet for a mean of 34.7 months (8). Approximately 30% tolerated the diet well and continued on it. Poor seizure control was a primary reason for stopping the diet in 43%. Three children were tapered off the diet after a mean of 28.5 months and continued to show a 75-100% seizure reduction from baseline pre-diet, suggesting either that the diet had a permanent effect or that the children's underlying seizure disorder had changed (8).

In addition, Bergqvist first reported a series of patients (n=3) with acquired epileptic aphasia that were successfully treated with the ketogenic diet (7). All three patients had lasting improvement of their language, behavior, and seizures for 26, 24, and 12 months, respectively (7). Even though the patient population is small, Bergqvist's study suggests a new therapeutic alternative for symptoms other than seizures in difficult-to-treat disorders.

The ketogenic diet has most commonly been used clinically as a treatment for seizures in children. This treatment seems appropriate for young human patients since several studies have shown that ketone bodies are utilized more efficiently in human fetuses, infants, and children when compared with adults (15). Despite the acceptance of the ketogenic diet as a viable option for pediatric patients with epilepsy, only recently have researchers begun to study the efficacy in adults. Sirven and colleagues' preliminary study of epileptic adults on a ketogenic diet reported that at 8 months of follow-up, 55% of the patients had a 50-90% decrease in seizure frequency, and 27% had a 90% seizure decrease (n=11) (16). Although several animal models report conflicting data regarding seizure resistance and its age dependency (11, 15), human studies show promising results for adult patients.

Traditionally, when patients initiate the ketogenic diet, they are started on the classic 4:1 diet in which there are 4 grams of fat for every gram of carbohydrate or protein. Despite the clinical success of this treatment, Bough and colleagues suggest that the conventional 4:1 ketogenic diet does not confer the greatest level of seizure protection in rat models (10). Instead, the study concludes that a 6:1 ketogenic diet, which shows no evidence of neurotoxicity, may be maximally efficacious in rats (10). Nevertheless, several other issues must be considered clinically (e.g. hypercholesterolemia, dietary compliance, etc.) that might argue against use of such high ketogenic ratios for human diets.

Diet complications

The ketogenic diet clearly does not provide the usual diet to which most people are accustomed, and there are many concerns about its nutritional adequacy and long-term complications. Even though the diet has proven to be effective in reducing the frequency of seizures in epileptic patients, it is not a therapy without risks and complications, and the actual and potential hazards must always be weighed against the benefits. Initiation of the diet can sometimes be difficult due to vomiting, hypoglycemia, dehydration and diet refusal (1, 17). Longer-term problems include kidney stones, constipation, acidosis/metabolic problems (particularly during illness), recurrent infections, atherosclerosis, cardiovascular disease, hypercholesterolemia, and feeding/nutrition problems (1, 17, 18). Additionally, the ketogenic diet may predispose a patient to hypercalcuria (18). Chesney et al. attribute this biochemical abnormality to fat malabsorption and/or little or no activity, both of which increase calcium reabsorption in the gut with subsequent urinary excretion (18). Furthermore, reduced fasting ketonemia has been shown to occur during simultaneous administration of valproate (a commonly used AED in the treatment of tonic-clonic seizures) and ketogenic diet treatment (3, 17).

Of additional concern is the obvious risk for developing cardiovascular disease due to long-term high triglyceride and cholesterol intake. A chart review of 45 children consuming the classic 4:1 ketogenic diet found that the average cholesterol and triglyceride concentrations were above the 95th percentile for age-matched controls (18). Although pancreatitis has been reported in children with elevated triglycerides, long-term complications of hyperlipidemia have not been established (18). The concern about long-term cardiovascular complications becomes even more pressing when one considers Bough's recommendation of increasing the ratio of fat to carbohydrates and protein (10).

The ketogenic diet was designed to provide relief from intractable seizures, and despite concerns that are raised about long-term complications, these risks seem less significant than the impact of hundreds of seizures a month and massive amounts of medication. In addition, it is important to stress that medical complications are infrequent reasons for stopping the diet. Thompson et al. found that only 6% of patients discontinued the diet for medical reasons (8), a multicenter study found that 12% had discontinued the diet for medical reasons (1), and Freeman et al. found that 7% had discontinued the diet because of illness (6).

Cost benefit analysis

A survey undertaken in a region of the United Kingdom during 1992 showed that although the new AEDs represented only 7% of prescriptions to people with epilepsy, they represented 39% of the total drug costs and accounted for one third of direct medical costs (19). Clearly, a reduction in AED usage would be financially beneficial. Long-term (12 months) implementation of a ketogenic diet may lead to a 74% decline in AED usage (20). In a prospective study of 150 children, 57% percent of the children stayed on the diet for 1 year and 74% of these children had their number of medications reduced (20). In the same study, 48% of children who stayed on the diet were on no medications at 12 months follow-up, and daily medication costs were reduced by nearly 70 percent (20). The actual cost reduction, as medications were tapered, was $530 per child, and the projected reduction in the second year was $920 per child (20).

Proposed Mechanisms

Given the long history of treatment with the ketogenic diet, and its truly remarkable efficacy in treating the most refractory of epileptic disorders in children, it is especially striking that we know so little about the underlying mechanism of the diet. Nevertheless, in recent years, significant advancements have been made towards uncovering the diet's method for seizure reduction. It was previously thought that the ketogenic diet's efficacy was directly associated with elevated levels of ketone bodies (acetoacetate [AA] and D-b-hydroxybutyrate [b-OHB]) in the blood (3). It was hypothesized that ketone bodies possess intrinsic anticonvulsant activity by directly altering neurotransmission because of structural similarities to g-aminobutyric acid (GABA). Several animal models, however, revealed a poor correlation between the level of ketonemia and seizure threshold, which strongly suggest that these two variables (b-OHB and seizure threshold) are independent consequences of the consumption of a ketogenic diet (10, 13). Furthermore, by

examining the effect of b-OHB and AA on excitatory and inhibitory synaptic transmission in rat hippocampal slices, it was demonstrated that ketone bodies do not directly alter synaptic transmission (21). Thio et al. concluded that if ketones have anticonvulsant properties, their site of action may not reside in the hippocampus (21).

Although they do not appear to directly affect synaptic transmission, another role for ketone bodies is supported by the finding that epileptic seizures alter the blood-brain barrier (BBB) properties. In epileptic brain tissue, cerebral blood flow is uncoupled from metabolic demand, due to a glucose transporter type 1 (GLUT1) defect as well as from potassium leakage across faulty tight junctions in the BBB (23). Increased extracellular potassium causes exaggerated neuronal firing, which ultimately leads to an increased metabolic demand. Increasing ketone bodies, due to the ketogenic diet, not only provides an alternative energy supply but also enhances GLUT1 activity (23). As a result, the energy deficit is partially compensated and ion homeostasis is re-established.

Another theory involves the accumulation of ketone bodies, thereby leading to a state of acidosis (or ketoacidosis). There is ample evidence to suggest that NMDA-type glutamate receptors participate in an important way in many forms of seizure activity, and that NMDA antagonism is often effective in blocking (or at least reducing) seizure activity (22). Since NMDA receptors are very pH sensitive, many researchers speculate that increasing ketoacidosis (due to a ketogenic diet) may impair involvement of NMDA-mediated transmission (22). Thus, if a ketogenic diet does lead to acidosis, then the diet's effect might be through the glutamate receptor system.

Conclusion

When considering the therapeutic effects of a treatment, it is always important and necessary to evaluate a patient's quality of life. Clearly the ketogenic diet exhibits beneficial results by decreasing (or eliminating) the frequency of epileptic seizures. Few serious complications of the diet have been reported (17), and the adverse effects are assumed to be tolerable since most patients remain on the diet at one year follow-up (6). Although diet maintenance is a burdensome task, the most common reason for discontinuing the diet is neither the lack of acceptance of the diet, nor the difficulty of diet preparation (6), thus further supporting the diet's tolerability. Furthermore, the ketogenic diet has been shown to reduce the number of prescribed medications as well as daily medication costs (19). Yearly individual savings can exceed $6000 (19), which can profoundly impact low-income families. Finally, a decline in AED usage may reduce the frequency of complications associated with simultaneous ketogenic diet and AED treatment, such as those seen with valproate and ketogenic diet use. Thus, the ketogenic diet has the potential to improve an epileptic patient's quality of life by enhancing various conditions.

Despite its increasing clinical use and demonstrated success, our understanding of how the ketogenic diet controls seizures is still incomplete. Additional long-term clinical trials and animal models should provide further insight into the mechanism underlying the diet's efficacy. Such studies might be able to answer why some patients continue to improve after the diet is discontinued. Other issues to address include the question of age-dependence and determining the most effective ratio (fats to carbohydrates and protein). With additional questions answered, perhaps the ketogenic diet will no longer be considered as an alternative therapy, but instead, the preferred method of treatment for epileptics.

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