Intractable Seizures in Children With Type 1 Diabetes: Implications of the Ketogenic Diet

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ABSTRACT

Introduction: The ketogenic diet is prescribed for seizures in some children with epilepsy. Children with type 1 diabetes are at risk for diabetic ketoacidosis caused by ketosis due to decreased insulin effect. Currently there are no clinical guidelines regarding the safety and efficacy of the ketogenic diet in patients with concurrent epilepsy and type 1 diabetes.

Objectives: This review examines the current literature regarding the association between type 1 diabetes and epilepsy, proposed mechanisms for the observed relationship, risks and benefits of the ketogenic diet, and clinical applications of the ketogenic diet in the context of type 1 diabetes and epilepsy.

Methods: PubMed was used to identify relevant articles. Key search terms included, "type 1 diabetes," "ketogenic diet," "seizure," "epilepsy," and "autoimmunity."

Results: There is an observed association between type 1 diabetes and epilepsy, with proposed mechanisms including genetic predisposition, anti-glutamic acid decarboxylase (GAD) antibodies, metabolic derangements and cerebrovascular damages. Case reports describe the use of the ketogenic diet for epilepsy management in children with diabetes with mixed results; however, there are no large, randomized controlled trials to evaluate the broader application of these findings.

Conclusions: In summary, there is inadequate evidence to support the use of the ketogenic diet in patients with coexisting epilepsy and type 1 diabetes in clinical practice. Further research is needed to determine the effectiveness, safety, and monitoring parameters of the ketogenic diet for these patients. The risks and benefits of the ketogenic diet as medical nutrition therapy for patients with both type 1 diabetes and epilepsy should be considered on an individualized basis.

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INTRODUCTION

There is a dearth of literature investigating the relationship between type 1 diabetes (T1D) and epilepsy. Several studies demonstrate that T1D is more common in patients with epilepsy when compared to the general population.[1-5] However, 1 study reported a similar prevalence of epilepsy in youth with T1D compared to the general population, refuting the suggestion that there is a relationship between these conditions.[6] That said, there are significant limitations in studying this relationship. First, missing laboratory and clinical data make determination of epileptiform versus secondary etiology (eg, hypoglycemia) of seizures difficult. Additionally, individuals with T1D may interface with health care more frequently, resulting in more readily diagnosed seizure disorders when compared to the general population. Regardless, the literature largely supports an association between these conditions; the exact underlying mechanism remains unclear.

The ketogenic diet is a well-studied, efficacious treatment for seizure disorders in a subset of pediatric patients.[7] It exhibits its antiseizure effects through multiple mechanisms that are poorly understood but include direct antiseizure effects of ketone bodies, ion channel regulation, mitochondrial changes, glycotic restriction, fatty acid oxidation, and anapleurosis.[8] There is also limited evidence that a low carbohydrate diet in a subset of T1D patients may improve glycemic control; the ketogenic diet is essentially a very low carbohydrate diet classically carried out in a 4:1 ratio of

fat to protein and carbohydrates.[9] This evidence raises the intriguing question of whether the ketogenic diet could be a safe and efficacious therapy to treat pediatric patients with a seizure disorder and concurrent T1D, while considering increased risk of diabetic ketoacidosis in a ketotic state. The purpose of this literature review is to (1) examine the current literature on the etiology of the association between T1D and epilepsy, (2) explore the risks and benefits of the ketogenic diet in pediatric patients with T1D, and (3) provide an overview of studies that have evaluated the ketogenic diet as concurrent treatment of epilepsy and T1D.

METHODS

The primary database used for this review was PubMed. All selected articles were written in English. There were no restrictions on publication dates of articles, but all selected articles were published within the last 15 years. Articles were identified using the search terms "type 1 diabetes," "ketogenic diet," "seizure," "epilepsy," and "autoimmunity."

RESULTS

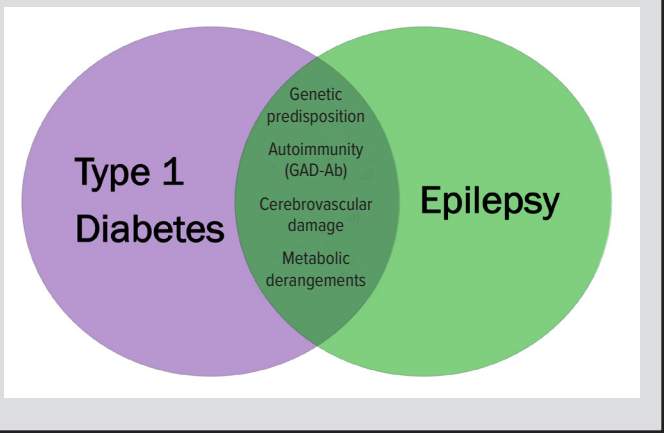
T1D and Epilepsy

There are 4 leading pathological mechanisms postulated to explain a relationship between T1D and epilepsy (Figure 1): genetic predisposition, anti-glutamic acid decarboxylase (GAD) antibodies, metabolic derangements (eg, hypoglycemia and hyperglycemia), and cerebrovascular damages.[10]

Epilepsy can be caused by either acquired or genetic pathologies (eg, receptor, ion channel defects).[11] T1D also is more common in individuals with first degree relatives with autoimmunity. A variable temporal sequence of T1D and epilepsy has been observed, suggesting a bidirectional relationship or a shared risk factor, such as genetic predisposition or autoimmunity.[12]

Shared autoimmunity between T1D and epilepsy, specifically anti-GAD antibodies (GAD-Ab), may play a role in the pathogenesis of these 2 conditions. GAD is an enzyme that catalyzes the conversion of glutamate, the primary excitatory neurotransmitter in the brain, to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. GAD is expressed in the brain as well as in pancreatic beta cells, where GABA is secreted as a paracrine signal molecule.[13] GAD-Ab are common in patients with T1D, detected in up to 80% of patients at diagnosis. Interestingly, GAD-Ab also are found in patients with neurological conditions, including stiff-person syndrome and epilepsy.[14] However, there are important antigenic differences identified between the epitopes recognized by GAD-Ab of diabetic patients and those of patients with neurological disorders.[15] A 2018 study analyzed GAD-Ab titers, epitope specificity, and enzyme inhibition in patients with several conditions, including epilepsy and T1D. Results showed some overlap among individuals with T1D and epilepsy, which could represent a more complicated continuum of autoimmunity.[16] Larger, longitudinal studies are needed to better understand the interaction among GAD-Ab, T1D, and epilepsy.

Figure 1. Potential Mechanisms for Association Between Type 1 Diabetes and Epilepsy



Metabolic derangements (eg, hypoglycemia and hyperglycemia) are common in T1D. These changes in blood glucose levels are thought to alter the balance between inhibitory and excitatory neuronal networks, ultimately predisposing these individuals to subsequently developing a seizure disorder.[14]

Lastly, the cerebrovascular changes in T1D and subsequent ischemia could predispose these individuals to seizures; however, this would predict an increased incidence of epilepsy in older type 2 diabetics, which has not been observed.[12] Additionally, many cases of epilepsy occur prior to T1D diagnosis, which is not consistent with a vascular etiology.[12] The underlying pathophysiology for the observed relationship between epilepsy and T1D remains unclear and continues to be an active area of research.

Benefits of the Ketogenic Diet in T1D

There are robust data to support the use of the ketogenic diet as treatment of epilepsy syndromes in patients >2 years old who have failed at least 2 antiepileptic drugs. The only absolute contraindications to the ketogenic diet are a limited number of metabolic diseases, including carnitine deficiency, beta-oxidation defects, and pyruvate carboxylase deficiency, among a few others.[17] Of note, T1D is not a standard contraindication to this dietary antiepileptic intervention despite obvious potential risks. In fact, the ketogenic diet has shown some promise in a subset of patients with nonautoimmune metabolic and endocrine disorders, including type 2 diabetes, obesity, metabolic syndrome, and polycystic ovarian syndrome. The ketogenic diet has been shown to have a favorable effect on caloric intake, body weight, lipid levels, glycemic indices, and insulin sensitivity.[18] It has not been extensively studied in pediatric populations with T1D, but a review article did look at the effects of a low carbohydrate diet (<45%) in individuals with T1D.[19] Three of the 8 studies that reported HbA1c found a statistically significant reduction, and 2

Table. Summary of Four Case Reports on Pediatric Patients with Type 1 Diabetes on Ketogenic Diets

Patient Description	Treatment Goals/ Insulin Regimen	HbA1c	Seizures on KD?	DKA on KD?	Other Clinical Outcomes
4-year-old girl with pyruvate kinase deficiency, static encephalopathy, seizure disorder. She was on KD > 1 year prior to T1D diagnosis (Henwood et al, 2006[21])	Serum ketones ≤ 2.5 mmol/L; glargine 0.3 - 0.53 U/kg at bedtime; lispro boluses as needed to maintain glycemic control	6.9% to 5.1% after 10 months on KD	Yes	No	Significant linear catch-up growth from <5% to 50%; achievement of new developmental milestones
3-year-old girl with epilepsy and T1D. Presented with right-sided spastic hemiparesis, tonic seizures, and developmental delay at 9 months. Diagnosed with T1D at 18 months (Dressler et al, 2010[20])	Unspecified ketosis goal 0.38 - 0.45 IU/kg insulin daily (unspecified formulation)	7.9% to 6.2% after 13 months on KD	No[a]	No	Advancement in developmental milestones; eventually stopped due to child refusal
2-year-old girl with epilepsy diagnosed at 4 months treated with KD; presented to ED in DKA, diagnosed with T1D (Aguirre et al, 2012[23])	Moderate urine ketones; glargine 0.3 U/kg at bedtime, aspart before meals if glucose > 200 mg/dL	7.3% to 7.2% after 10 months on KD	No	No	Difficulty managing hypoglycemia
3-year-old male diagnosed with T1D, subsequently presented with generalized tonic-clonic seizure 1 week later; KD initiated via gastrostomy tube (Aylward et al, 2014[22])	Blood ketones ≥ 4.0 mmol/L, Target capillary glucose 4 - 10 mmol/L; unspecified insulin regimen	5.7% to 6.4% while on KD	Yes[b]	No	Improved cognitive functioning

Abbreviations: KD, ketogenic diet; DKA, diabetic ketoacidosis; T1D, type 1 diabetes; ED, emergency department.
[a]4-month follow-up EEG showed no evidence of seizures, although future electroencephalograms showed subclinical seizure patterns.
[b]Patient had no observed drop attacks or myoclonic astatic seizures on KD but continued to have occasional brief nocturnal seizures.

of 5 studies that reported daily insulin usage reported significant reductions in total daily dose in the low carbohydrate groups. In addition, 4 case reports exhibited favorable effects on blood sugar control.[20-23] More research is needed to clarify the effects of a low carbohydrate diet and specifically the ketogenic diet on blood sugar control in T1D.[19] If the ketogenic diet is found to improve HbA1c levels in certain patients without adding too much risk (diabetic ketoacidosis, poor growth, etc) it could decrease the need for insulin and one could potentially treat T1D and epilepsy with 1 intervention.

Risks of the Ketogenic Diet in T1D

The ketogenic diet was feasible and efficacious as an antiepileptic in 4 case reports (Table). However, the authors also report significant risks, citing hypoglycemia, diabetic ketoacidosis, poor palatability, and attenuated growth and development.[20-23]

Hypoglycemia

By nature of the therapy, the ketogenic diet is a low carbohydrate diet that increases the risk of low blood sugar—already a risk in T1D due to exogenous insulin. It is not uncommon for children on the ketogenic diet to have blood glucose < 70 mg/dL, which is often the treatment threshold for hypoglycemia in T1D. Necessary treatment of low blood glucose in children with T1D and seizures attenuates the therapeutic, antiepileptic effect of the ketogenic diet.[23] Additionally, in the case of severe hypoglycemia, there would likely be a blunted response to glucagon in an individual in therapeutic ketosis and increased risk of hypoglycemic seizure.

Diabetic Ketoacidosis

It can be challenging to differentiate therapeutic ketosis from diabetic ketoacidosis; it is difficult to interpret ketone levels in these individuals. There is no consensus regarding an acceptable level of ketosis for pediatric patients with T1D on the ketogenic diet.[9] Theoretically, there are important differences in lab values between the ketogenic diet and diabetic ketoacidosis. In therapeutic ketosis, blood glucose should be normal or low/normal, ketone body concentration should be 7-8 mmol/L, and pH should be normal, whereas in diabetic ketoacidosis, blood glucose is variable, ketone concentration will be elevated (> 25 mmol/L), and pH will be low (< 7.3).[24] However, developing diabetic ketoacidosis starts with a similar, mild/moderate ketosis, and it is at this point that intervention is critical and can prevent severe diabetic ketoacidosis, which has life-threatening complications. Distinction between ketone levels from therapeutic ketosis in the ketogenic diet and developing diabetic ketoacidosis may be difficult to detect outside of the medical setting. It is also possible that following the ketogenic diet could increase the possibility or tempo of developing severe diabetic ketoacidosis by having more ketones at baseline.

Poor Palatability

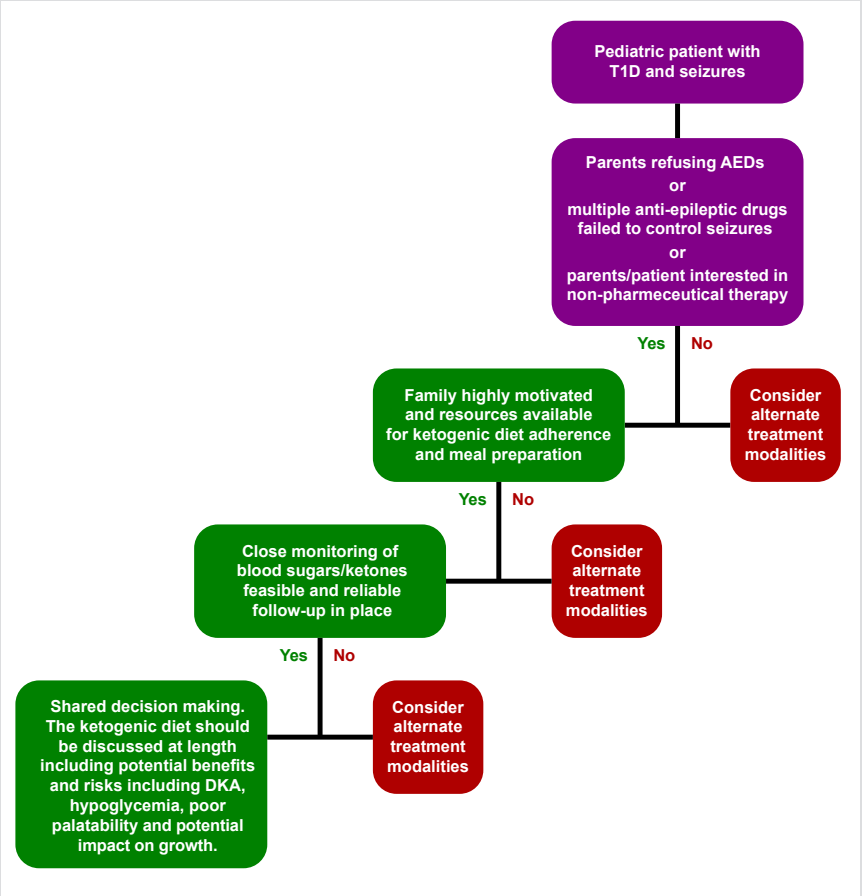
Several of the case studies described identified issues of palatability, which are common in dietary interventions. In 2 studies, the ketogenic diet was stopped due to poor palpability or child refusal, despite the beneficial effects from the diet therapy.[20,23] It is understandable that children may not adhere to such a limited diet, especially as they get older and are offered more choices and develop food preferences. The ketogenic diet may be a more feasible option in children who are—for unrelated reasons—gastronomy-tube dependent, as formulas can be selected based on their

nutritional content and avoid the issue of poor palatability. Additionally, there are numerous websites and cookbooks that offer a variety of recipes for meals, snacks, and desserts that meet ketogenic diet limitations. However, significant time and cost is required for ketogenic meal preparation, and this may not be compatible with families' lifestyles.

Poor Growth

Significant dietary changes have potential effects on growth and development in pediatric patients. T1D guidelines recommend a well-balanced diet with 50% to 55% of energy derived from carbohydrates—much higher than recommended in the ketogenic diet.[25] A case series of 6 children with T1D who adopted a low carbohydrate diet of varying degrees had consequences, including poor growth, an unfavorable lipid profile, generalized fatigue, and mental health comorbidities.[26] However, other studies have reported significant linear catch-up growth[21] and advancement in developmental or cognitive function[20-22] after initiation of the ketogenic diet. The risk of growth effects from the ketogenic diet should be thoughtfully considered on an individual basis.

Figure 2. Framework for Clinical Considerations for Initiating the Ketogenic Diet in a Pediatric Patient With Type 1 Diabetes and Seizures



Ketogenic Diet in Patients with Epilepsy and TID

There are 4 case reports to date that attempt to examine the safety and efficacy of the ketogenic diet in patients with concurrent epilepsy and T1D (Table).[20-23] Although these case studies present examples of the ketogenic diet treating seizure disorders with improved HbA1c levels in some pediatric patients with T1D, there are no case-control cohort studies or systematic reviews on this topic. Furthermore, with the potential significant risks of the ketogenic diet in pediatric patients with T1D, it may be unethical to study this potential therapy in a large, blinded, randomized controlled trial.

CONCLUSIONS

The mechanism of the connection between T1D and seizure disorders is unclear, but genetic predisposition, anti-GAD antibodies, metabolic derangements (ie, hypoglycemia and hyperglycemia), and cerebrovascular damages may contribute. There is anecdotal evidence in the form of case reports that supports the feasibility and efficacy of the ketogenic diet as therapy in children with both epilepsy and T1D, but no randomized controlled trials exist to rigorously evaluate the broader application of these findings. In summary, the risks and benefits of the ketogenic diet as medical nutrition therapy for patients with both T1D and epilepsy should be considered on an individualized basis (Figure 2). Clinicians should inform families considering this treatment modality of the clinical risks and intensive monitoring required.

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