# Refractory epilepsy and the ketogenic diet: Pathophysiological aspects and possible implications in dental practice

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## Abstract

Epilepsy denotes any disorder characterized by recurrent seizures due to abnormal paroxysmal neuronal discharge in the brain. Symptoms range from sensory absences to convulsive movements and loss of consciousness. Antiepileptic drugs are the first line of treatment. However, 20% individuals with epilepsy have drug-resistant seizures despite optimal treatment. For those with refractory epilepsy, the ketogenic diet is an effective alternative therapeutic approach. The ketogenic diet is a high-fat, low-carbohydrate, and adequate-protein diet that mimics the biochemical effects of fasting. There are many disparate mechanistic theories of how this diet protects against seizures. Key insights indicate that it has effects on intermediary metabolism that influence the dynamics of the major inhibitory and excitatory neurotransmitter systems in brain. This paper discusses the implicitly significant and diverse biochemical changes affected by this unique therapeutic approach that may have a bearing on oral health and the delivery of dental care to individuals with refractory epilepsy.

## Key words

Ketogenic diet, oral health, refractory epilepsy, therapeutic ketosis

## Introduction

Epilepsy is a serious neurological disorder with no racial, social class, or geographic boundaries. It is a condition with heterogeneous symptoms characterized by recurrent seizures.[1] Epilepsy is diagnosed when a person has two or more unprovoked seizures.[2] A seizure manifests as an episodic disturbance of movement, feeling, or consciousness, resulting from abnormal discharge of cerebral neurons.[3] The causes of epilepsy are extremely diverse, encompassing genetic, developmental, infectious, traumatic, neoplastic, and degenerative disease processes, with the likely cause in individual patients related to the age of onset. It has its first peak in childhood and a second peak in elderly patients.[4] Worldwide, epilepsy is a significant cause of disability and disease burden[5] and accounts for 1% of the global burden of disease.[6] Epidemiological data also indicate that recurrent, spontaneous, unprovoked seizures associated with epilepsy occur in 1 to 3% of children, with the highest incidence in the first year of life.[7,8] Most of these children are successfully treated for the condition by antiepileptic drugs (AEDs). In about 10 to 40% of these children, however, epilepsy remains uncontrolled despite drug treatment, and such cases are labeled as having refractory or intractable epilepsy.[9-11] Interestingly, whatever the cause of the intractability, most cases with refractory epilepsy have one thing that is common: they are refractory to most or all AEDs. Because drug-resistant recurrent seizures adversely affect early brain development, spatial

learning, and memory, there is a need for alternative therapies in this subgroup of patients.[12] These include the ketogenic diet, vagal nerve stimulation, and surgery.[13] This article discusses the possible implications of this non-pharmacological approach for the management of drug-resistant epilepsy in dentistry.

## Intractable Epilepsy

Epilepsy is a symptom of cerebral dysfunction[14] and for this symptom to appear, a population of epileptic neurons must exist within the CNS. These neurons are subject to paroxysmal depolarization shifts that render them hyperexcitable. Hyperexcitable neurons may be limited to a specific area of the CNS, as in localization-related epilepsies, or may represent a widely distributed pattern involving neuron networks with diminished inhibition or excessive excitation, as in generalized epilepsies.[15] This is a dynamic disease process and reflects complex anatomical and physiological changes in the presence of environmental and genetic factors.[16] The first line of treatment of epileptogenesis and the end product of this disease process, i.e., seizures, is pharmacological suppression or prevention with specific drugs. The response to medical treatment, however, is influenced by certain factors such as the age of onset, the type of epilepsy diagnosed, anatomical abnormalities of the neural architecture, metabolic disorders, and genetic conditions; and these factors in unison or isolation will determine the development of intractability in a patient.[17] There is no universal agreement as to how frequently and over what period of time seizures must occur to constitute intractability, since seizure frequency used by different investigators in defining intractability ranges from one per month to one per year. Nevertheless, intractability may be defined as seizures which have not been completely controlled with AED one year after onset, despite accurate diagnosis and carefully monitored treatment.[16]

## The Ketogenic Diet: A Historical Perspective

The ketogenic diet is an effective non-pharmacological treatment modality for treating pharmacoresistant forms of common epilepsies and difficult to treat catastrophic epilepsy syndromes of infancy and early[18] epileptic encephalopathies. Although the diet is useful in people of all ages, clinical experience suggests that it may be more useful in children because adults have more difficulty in adhering to it.[19] However, there are biblical references to the salutary effects of starvation on seizure control.[20] It was only in 1921, at the convention of the American Medical Association, that the effectiveness of this approach in treating epilepsy was reported to the scientific community.[21] Building on the research of investigators at John Hopkins, Wilder, at the Mayo Clinic, proposed attempting an actual diet and coined the term *ketogenic diet* to describe a diet that produced a high level of ketones in the blood through an excess of fat and lack of carbohydrate. However, it was Peterman, a colleague of Wilder, who first proposed the testing of this diet on a few epilepsy patients and was the first to use the ketogenic diet as a treatment for epilepsy. The diet first proposed by her is virtually identical to the diet being used today. With the appearance of Dilantin on the scene in the 1930s, the focus shifted toward pharmacological management of epilepsy. Over the years, the use of this approach in treating epilepsies became polarized with some abandoning it for newer and probably more effective pharmacotherapeutic interventions, and others continuing to use this diet. However, an event in the 1990s that led to the creation of the Charlie Foundation and the results of two prospective uncontrolled studies reaffirmed the usefulness of the diet in the medical mainstream.[21] There are three types of ketogenic diets, the Classic Diet as proposed in the 1920s, the MCT (Medium Chain Triglycerides) Diet proposed by Huttenlocher in the 1970s (the ketogenic diet), and the Radcliffe Infirmary Diet which is a combination of the traditional and the MCT diet.[22] Although a discussion on the advantages and disadvantages of these diets is beyond the scope of this article, a common denominator of all these approaches is the versatility of this non-pharmacologic treatment alternative in improving the quality of life of refractory patients.[23]

## Ketogenic Diet: Mechanisms of Action

Despite nearly a century of use, the understanding of the mechanisms underlying the clinical efficacy of this therapeutic approach in the treatment of pharmacologically resistant epilepsies is still nebulous, and many seemingly disparate mechanistic theories have been proposed.[24] In the backdrop of these theories, one intersecting view formed by gleaning at the literature is on the role of ketone bodies, fatty acids, and limited carbohydrates in controlling seizures. The consumption of the ketogenic diet in any of its forms over a period produces a characteristic elevation in the

circulating levels of ketone bodies.[19] This chronic ketosis is anticipated to modify the tricarboxcylic acid cycle to increase gamma amino butyric acid synthesis, limit the generation of reactive oxygen species (ROS), and boost energy production in the brain. Among several direct neuroinhibitory actions, polyunsaturated fatty acids increased after a ketogenic diet induces the expression of neuronal uncoupling proteins, a collective upregulation of numerous energy metabolism genes and mitochondrial biogenesis. These effects further limit ROS generation and increase energy production. As a result of limited glucose and enhanced oxidative phosphorylation, reduced glycolytic flux is hypothesized to activate metabolic K(ATP) channels and hyperpolarize neurons and/or glia. Although no single mechanism can explain the positive clinical effects, these seemingly diverse but coordinated changes seem poised to stabilize synaptic function and increase the resistance to seizures throughout the brain.[24]

## The Patient on a Ketogenic Diet: Possible Implications in Dental Practice

Epilepsy is one of the most common neurological disorders diagnosed in children.[25] Childhood-onset epilepsies can be divided into benign, intermediate, and catastrophic [Table 1], based on their impact on childhood development.[26] It is in the catastrophic epilepsies where the response to AEDs is inconsistent that the ketogenic diet has proven to be an effective treatment strategy. There is accumulating evidence to suggest that this diet has antiepileptogenic properties that extend beyond its disease-modifying activity.[19] The ketogenic diet mimics biochemical effects of fasting, and thus, it is deficient in most vitamins, minerals, and probably trace elements.[27] A review of the pertinent literature on the complications associated with this dietary intervention that has largely been reported in the form of case reports indicates that most oral and systemic complications are related to a certain deficiency state. Once the condition was investigated and corrective measures instituted, the condition in most of the cases was successfully reversed. This means that those clinicians who use this diet must be fully aware of the potentially serious adverse affects, and should also be able to advise those providing adjunctive care on the possible implications of this diet. Clearly, there is need for multidisciplinary management of patients with intractable epilepsy on a ketogenic diet. Complications that might occur are wide ranging, including scurvy leading to persistent bleeding from the gums,[14] changes in platelet function with excessive bruising[28] to more serious conditions such as severe hypoproteinemia, lipemia, renal tubular acidosis, and marked elevation of all liver function tests.[29] It has also been reported that patients on a ketogenic diet exhibit a decrease in bone mass due to disordered mineral metabolism with features of vitamin D deficiency osteomalacia[30] and a definite susceptibility to fractures.[31] The ketogenic diet also causes cardiac complications by different mechanisms that include selenium deficiency[27] and low serum bicarbonate and high beta hydroxybutyrate. These can lead to changes ranging from electrocardiographic abnormalities including QT prolongation to gross pathologically significant anatomical changes such as severe dilatation cardiomyopathy.[32,33] Because of the significant changes in their blood biochemistry and physiology, children on this therapeutic regimen would probably be best treated for their dental ailments in a hospital setting by a specialist, with perioperative monitoring of serum pH, glucose, and bicarbonate, and with special attention to the epileptogenic potential of some anesthetic agents.[34,35] It is generally believed that children with many chronic childhood illnesses, including epilepsy, are at a higher caries risk, because they are usually on long-term medications that may contain sugar and also because effective dental hygiene may be difficult to achieve.[36] However, data on the oral health status of children with epilepsy, especially pharmacoresistant forms of epilepsy, are scarce.[37,38] The ketogenic diet is designed to be low in carbohydrates, adequate in proteins, and high in fats so as to induce a state of therapeutic ketosis for children with refractory epilepsy. It is important for care providers to understand that to maintain this ketotic state, patients must restrict their carbohydrate intake. These patients often require over-the-counter and prescription medications, especially liquid formulations that might contain significant quantities of carbohydrates, which might go unrecognized, and could lead to potential

**Table 1: Catastrophic epilepsies (epileptic encephalopathies) in which ketogenic diet has been found to be effective**

| |
|---|
| Dravet syndrome[43] |
| Early myoclonic encephalopathy[44] |
| Landau Kleffner syndrome[44,45] |
| Lennox-Gastaut syndrome[45,46] |
| Doose epilepsy[46,47] |
| Dravet syndrome[46] |
| Rett syndrome[46] |

loss of seizure control.[39-41] It has been suggested that these children should be dispensed tablets or capsules and sugar-free liquid medications wherever possible and if a sugar-free substitute is not available, then the carbohydrate content of these medications should be taken into account and adjustments made in the diet.[36] An aspect of this diet that warrants investigation is its indirect effect on the dental caries and periodontal disease status of individuals on this diet. This is an essentially noncariogenic diet in which virtually all cariogenic substrates have been eliminated. Also, the changes induced by this diet at the biochemical level cause chronic ketosis, leading to limited generation of ROS, an active biomarker in periodontal disease.

## Conclusions

The ketogenic diet is a unique therapeutic modality which has decidedly salutary effects in controlling refractory forms of epilepsy, especially in children. This intervention has profound multiple effects at the biochemical level that are not completely understood and may affect different body systems. This may not only pose a risk in imparting dental care but may inherently affect the manifestation of dental caries and periodontal disease. This emphasizes the need to recognize that children on this diet have a "dental special need."

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