

Association Between Hyperglycemia and Epilepsy: From Clinical Implication to Therapeutics

¹Shreya Patel, ¹Shannon Kim, ¹Suhrud Pathak, ^{1,2}Jeyaram Bharathi Jeyabalan, ¹Keyi Liu, ¹Rishi Nadar, ³Jun Ren, ¹Timothy Moore and ¹Muralikrishnan Dhanasekaran

¹Department of Drug Discovery and Development, Harrison College of Pharmacy, Auburn University, Auburn, AL 36849, United States

²Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Nilgiris, Ooty, Tamil Nadu, 643001, India

³Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital Fudan University, 200032, Shanghai, China

ABSTRACT

Epilepsy and hyperglycemia are significant pathologies that are increasingly recognized to have an interlinked relationship. Epidemiological data highlights the growing prevalence of concurrent diabetes mellitus (DM) and epilepsy, emphasizing the need for tailored management strategies. Therefore, this study explores the complex association between hyperglycemia (particularly DM) and epilepsy. The Google Scholar, PubMed (NIH), CDC and WHO databases were searched using an advanced search feature manually through the second week of April 2024 for Journal articles, books and book chapters were manually searched under all languages without filter restrictions. The keywords used for the search are given below. This review delves into the pathogenesis of hyperglycemia-induced changes in brain function, including alterations in neurotransmitter activity, electrolyte imbalances and effects on neuronal excitability. The coexistence of DM and epilepsy presents clinical challenges, as certain antiepileptic medications can impact glycemic control and vice versa. The review examines the epidemiology of these coexisting conditions, focusing on risk factors, age of onset and potential comorbidities. The intricate pathways linking hyperglycemia to seizures, including the role of glutamate and ionotropic receptors, are dissected, shedding light on the mechanisms behind epileptic episodes in DM patients. This study highlights the vulnerability to seizures in T1DM patients due to cerebrovascular dysfunctions and altered seizure thresholds in specific brain structures. Furthermore, the management approaches for these comorbid conditions are discussed, encompassing non-pharmacological interventions such as lifestyle modifications and pharmacological treatments targeting both epilepsy and hyperglycemia. This comprehensive review synthesizes current knowledge on the intricate relationship between hyperglycemia and epilepsy in DM patients. The elucidation of underlying mechanisms and the development of effective management strategies are crucial to improving clinical outcomes in this growing patient population. Further research is needed to understand the intricacies of the connection and to improve treatment procedures for those who have DM and epilepsy.

KEYWORDS

Hyperglycemia, epilepsy, clinical implication, therapeutics, iatrogenesis

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INTRODUCTION

Epilepsy is a chronic neurological condition characterized by recurrent seizures. It can occur in all ages of the population and has been known to have significant impacts on the mental and physical well-being of patients¹. Hyperglycemia, on the other hand, is a condition characterized by high blood sugar levels² and is a hallmark of diabetes mellitus (DM)³, a metabolic condition with a range of effects, including cognitive deficits, cardiovascular disease and kidney disease^{4,5}. Hyperglycemia often induces cellular damage and death deleterious enough that it cannot be readily repaired by the body's natural mechanisms⁶. Recent evidence has established a strong association between hyperglycemia and seizure episodes in patients with DM, which is deemed to be more than just coincidental. In fact, approximately 25% of patients with diabetes are expected to experience seizures². Further, diabetic patients who experience Diabetic Ketoacidosis (DKA), a hyperglycemic emergency characterized by increased blood glucose levels, elevated urinary/blood ketoacids and high anion gap metabolic acidosis⁷, also experience seizures more frequently². Series of case reports have affirmed the circadian instability associated with hyperglycemia that majorly affects the sleep-wake cycle in patients with DM⁸⁻¹¹. It was also reported that sleep disorders are significantly more persistent in patients with DM as compared to those without diabetes¹²⁻¹⁵. There has long been a strong belief that the hyperarousal idea of neurons is a concerning etiological element in insomnia and there has been thorough scientific investigation into both the source and impact of this conception¹⁶⁻¹⁹. Similar to this, natural development and function are impacted and damaged by the circadian contributions to and reactions from persistent hyperarousal. To counterbalance neuronal firing, neural plasticity in dysregulated circumstances allocates resources to hyper-activated neuronal networks, compensates for neural recovery and maintains intrinsic system stability^{11,20}.

About 30% of individuals with Temporal Lobe Epilepsy (TLE) are resistant to standard antiepileptic medications, despite the fact that some antiepileptics have been shown to be effective in stopping or reducing the frequency of epileptic episodes²¹. In addition to conventional antiepileptic medication, targeting and controlling glucose levels in DM patients may offer a cutting-edge and effective alternative treatment approach for treating seizures¹¹. A meta-analysis performed to explore the association between hyperglycemia and epilepsy provides recommendations for managing these coexisting conditions.

Epidemiology: The DM and epilepsy are two chronic conditions affecting millions of individuals worldwide. With regards to diabetes mellitus/insipidus, it is estimated that approximately 537 million populations are afflicted worldwide, with diabetes mellitus being the most predominant form²². The prevalence of DM is increasing at an alarming rate, with an estimated 1 in 11 adults by 2040. On the other hand, epilepsy is estimated to affect approximately 50 million patients globally^{23,24}.

The coexistence of diabetes mellitus and epilepsy is becoming increasingly common and the epidemiology of this population is of growing interest²⁵. Studies have shown that people with diabetes mellitus have an elevated risk of developing epilepsy and conversely, people with epilepsy have a higher risk of developing diabetes mellitus²⁶. The prevalence of both conditions is higher in low- and middle-income countries. The age of onset of diabetes mellitus and epilepsy is similar, with a higher incidence in children/adolescents and older adults²⁷. There is also an increased prevalence of comorbidities such as hypertension and other cardiovascular disease in patients with such coexistence²⁸. Management of patients with concurrent diabetes mellitus and epilepsy can be challenging, as certain antiepileptic medications can worsen glycemic control²⁹⁻³¹, while some antihyperglycemics can attenuate seizure threshold³²⁻³⁴. Understanding the epidemiology of patients with concurrent diabetes mellitus and epilepsy is essential for optimal management strategies and clinical outcomes in this patient population³⁵.

Pathogenesis of hyperglycemia and epilepsy: Though the precise pathogenesis of seizures associated with DM remains undetermined, several known mechanisms do exist that support the hypothesis that hyperglycemia can lead to changes in brain function, including alterations in electrical activity, which can trigger seizure episodes in patients with epilepsy³⁶. Glutamate, an excitatory neurotransmitter, is more abundant in the central nervous system³⁷. Ionotropic glutamate receptors include N-methyl-d-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite and delta receptors classified based on sequence similarity and ligand specificities³⁸.

Over-activation of N-methyl-D-aspartate (NMDA) receptors, which are ionotropic glutamate receptors, impairs neurons in the nervous system. Although it has been suggested that NMDA receptor activation aids in the progression of diabetes mellitus, little is known about the impact of excessive long-term NMDAR activity on β -cells, particularly with episodes of hyperglycemia. One study established that an increase in glutamate, an excitatory neurotransmitter, may accelerate the malfunction and apoptosis caused by hyperglycemia in β -cells, contributing to the progression of diabetes mellitus³⁹. Endogenous glutamate exacerbates the high-glucose-induced dysfunction of β -cells in diabetes by over-activating NMDA receptors on β -cells, which in turn activates NF- κ B and NLRP3 inflammasomes. Early alterations in AMPA receptor subunits, primarily in the GluA2 subunit, are induced by high glucose concentration in retinal neuron cells. In contrast, it appears that the expression of AMPA receptors in hippocampus neurons is unaffected by high glucose levels, indicating that retinal cells are more vulnerable to the stress brought on by high glucose levels than hippocampal neurons.

Thirty to forty percent of cerebral synapses implement GABA, the brain's primary inhibitory neurotransmitter, to promote inhibition and, by limiting nerve transmission, to lower neuronal excitability⁴⁰. The GABA is synthesized when glutamic acid decarboxylase (GAD) transforms L-glutamate. GABAergic inhibition of the dorsal motor nucleus of the vagus (DMV) neurons changes substantially after chronic hyperglycemia/hypo-insulinemia, which may play a role in the autonomic dysfunction associated with diabetes³⁸. The vagus nerve, a cranial nerve that is essential in controlling the parasympathetic nervous system, has DMV as a key component. The DMV is in possession of regulating the parasympathetic nervous system's efferent (motor) impulses that are carried to the heart, lungs, gastrointestinal tract and other visceral tissues⁴¹. The effects of DMV inhibition on autonomic systems and physiological functioning can be profound²⁵. The degree and length of inhibition and the conditions in which it transpires may all affect the specific effects, as with any intervention affecting neural networks. According to one case study, people with diabetes mellitus exhibit alterations to their GABAergic neurotransmitter system, which are linked to deficit cognitive performance. The principal findings indicated that those with diabetes mellitus, higher fasting blood glucose levels and higher glycosylated hemoglobin levels, as well as those with worse cognitive function, all had greater GABA concentrations. Mechanical hyperalgesia and depolarization of the resting membrane potential of primary nociceptive neurons are triggered by hyperglycemia³⁹. Hyperglycemia delays terminal depolarization in the ischemic core and facilitates faster repolarization in severely malperfused penumbral tissue after spreading depression because it increases the availability of energy substrates in this state.

Alongside the neurotransmitters and receptor stimulation, hyperglycemia is also linked to electrolyte imbalance, especially sodium (hyponatremia) and calcium (hypercalcemia), that are linked with augmented morbidity and mortality^{42,43}. Patients with diabetes often experience hyponatremia, or reduced blood sodium levels, which can be linked to a variety of underlying pathogenetic causes^{41,44,45}. Patients with poorly controlled diabetes mellitus have varying serum sodium levels because these levels can occasionally be attributed to hyponatremia caused by hyperglycemia, hypotonic losses caused by osmotic

diuresis, which tends to raise serum sodium levels and hypovolemia-induced decrease in serum sodium levels^{46,47}. Reduced risk of adverse effects such as falling, impaired gait and cognitive impairment is linked to even the smallest drops in blood salt levels⁴⁸. Hyponatremia in DM patients is also attributed to the use of thiazide diuretics^{49,50} and first generation sulfonylureas (tolbutamide and chlorpropamide)^{51,52} which leads to sodium loss in urine²⁷. Though the incidence of primary hyperparathyroidism in DM is less than 1%, elevation of the serum calcium level is closely associated with a variety of conditions linked to hyperparathyroidism^{53,54}. Long-term insulin resistance or insufficiency can cause hyperparathyroidism, which can worsen glycemic dysregulation in the development of diabetes mellitus or cause DM itself³⁶. The primary neurological symptoms of hypercalcemia are weakness, disorientation, sleepiness and lethargy³⁸. Additionally, the onset of seizures is thought to have been caused by vasoconstriction and hypertensive encephalopathy brought on by hypercalcemia^{55,56}. Therefore, seizures, which may be the only presenting symptom, can be a fast-progressing neurologic sign of severe or acute electrolyte imbalances linked to diabetes mellitus. Additionally, hyperglycemia can cause damage to blood vessels in the brain, leading to the development of epilepsy. Individuals with epilepsy pose a higher risk of developing hyperglycemia due to antiepileptic therapy, which itself can cause insulin resistance and impair glucose metabolism⁵⁷.

Supportive data: Several studies have investigated the relationship between epilepsy and hyperglycemia, particularly in individuals with type 1 diabetes mellitus (T1DM). These studies faced challenges in distinguishing unprovoked epileptic seizures from seizures caused by metabolic dysfunctions like hypoglycemia. In some instances, comprehensive clinical details or metabolic studies for all participants were not fully accessible. Despite these limitations, the research indicated that individuals with T1DM are at a higher risk of epilepsy compared to the general population, with the risk ranging from two to six times greater. This elevated risk persists even among patients below 18 years of age, although some research groups were unable to confirm this outcome.

The prevalence of epilepsy in individuals with T1DM varies between 8.7 and 21 per 1000 individuals, with T1DM occurring two to four times more frequently in patients with idiopathic generalized epilepsy compared to the general population. Additionally, two different cohorts, one in the United Kingdom and the other in Taiwan, found a higher incidence of epilepsy in patients with T1DM compared to control groups.

On average, T1DM typically develops 1.5-2.8 years prior to the onset of epilepsy. Specific risk factors for epilepsy occurrence in individuals with T1DM include a younger age and an earlier age of diabetes onset. The risk of ketoacidosis doubles in individuals with both T1DM and epilepsy, regardless of the antiepileptic drugs used for treatment. However, no notable differences were found in metabolic control, insulin treatment schedules and doses, or the presence of beta cell-specific autoantibodies between individuals with comorbid T1DM and epilepsy and those with T1DM alone.

Hyperglycemia poses a significant risk for focal seizures in individuals with T1DM due to heightened vulnerability to cerebrovascular dysfunctions. These dysfunctions are exacerbated by neuronal hyperosmolarity, dehydration and a subsequent decrease in cerebral blood flow. Certain cerebral structures, including the frontal or occipital cortex, amygdala and hippocampus, exhibit a lower seizure threshold in response to glucose level fluctuations, increasing the occurrence of seizures in T1DM patients, particularly those with pre-existing structural lesions disrupting regional neuronal activity.

The correlation between T1DM and an increased likelihood of ketoacidosis in epilepsy patients remains unclear and requires further investigation. This finding contradicts the perceived anticonvulsant effects

attributed to ketosis, which are independent of diabetes-related factors such as those observed with ketogenic diets or specific antiepileptic treatments. Proposed mechanisms for this phenomenon include the use of carbonic anhydrase inhibitors in antiepileptic treatments or malfunctions in mitochondrial respiratory chain enzymes.

Hypoglycemia, whether acute or chronic, may serve as a triggering factor for seizures in T1DM patients undergoing insulin therapy. Individuals with recurrent hypoglycemic episodes have a heightened risk of epilepsy compared to euglycemic individuals. Acute seizures resulting from hypoglycemia are linked to functional and structural damage, causing increased cortical excitability due to the brain's insufficient energy supply from glucose. Preclinical studies suggest a potential role of glutamate-related excitotoxicity resulting from reduced glucose availability, leading to EEG abnormalities or unprovoked seizures. Adaptive mechanisms may be activated in cases of recurrent hypoglycemia, utilizing alternative energy sources such as lactate, which can increase susceptibility to epilepsy⁵⁸.

Management: Regarding management, there are currently no specific criteria or guidelines for managing both hyperglycemia and epilepsy concurrently. However, recent literature suggests practical approaches, including regular blood sugar monitoring, lifestyle changes to improve glucose control, such as regular exercise, a healthy diet and stress-reducing activities. While antiepileptic drugs are commonly assumed necessary, recent studies emphasize the importance of antidiabetic therapy in managing hyperglycemia and epilepsy. Although antiepileptic drugs may be used, the focus remains on managing blood glucose levels and antiepileptic therapy should be adjusted as necessary to reduce the risk of hyperglycemia. For non-pharmacological therapy, recent research shows that the management of hyperglycemia in people with epilepsy should involve monitoring blood sugar levels regularly and making lifestyle changes to improve glucose control. This includes engaging in regular exercise, eating a healthy diet, avoiding triggers that can cause seizures and engaging in stress-reducing activities such as meditation and yoga²⁸.

When it comes to pharmacologic management, recent studies showed that the role of antiepileptic drugs is not nearly as important as the role of antidiabetic therapy in patients with hyperglycemia and epilepsy. Most individuals with diabetes who have partial epilepsy are resistant to regularly prescribed antiepileptic medications despite the widespread belief that treating these patients with antiepileptic medicines is essential^{2,59}. On the other hand, diazepam can be used to treat partial status epilepticus and certain DM patients with epilepsy have been shown to respond well to carbamazepine¹¹. Anti-diabetic medications, however, are seen to be the most crucial elements in the management of the disease²⁴. Even after antiepileptic medications are stopped, individuals can no longer have seizures when their blood glucose levels progressively return to normal. If antiepileptic drugs are used in treatment, studies still recommend a focus on managing blood glucose levels and antiepileptic therapy should be adjusted as necessary to reduce the risk of hyperglycemia²¹. The therapeutic approach for managing epilepsy in patients with type 1 diabetes (T1DM) is like that of patients without T1DM. The principles of diabetes therapy, including insulin use, nutritional recommendations and physical activity, can also have notable positive effects on seizures by ensuring optimal metabolic control⁵⁹.

The ketogenic diet has been observed to effectively control seizures in a small number of documented patients with diabetes, without increasing the risk of hypoglycemia or complicated ketoacidosis^{28,60,61}. A 3-year-old boy with myoclonic-astatic epilepsy, a 4-year-old boy with pyruvate dehydrogenase deficiency who developed type 1 diabetes mellitus (T1DM) after beginning the diet, a bilateral watershed infarcts in migration disorder were among the cases that were reported^{28,62}. it might be difficult to discern between

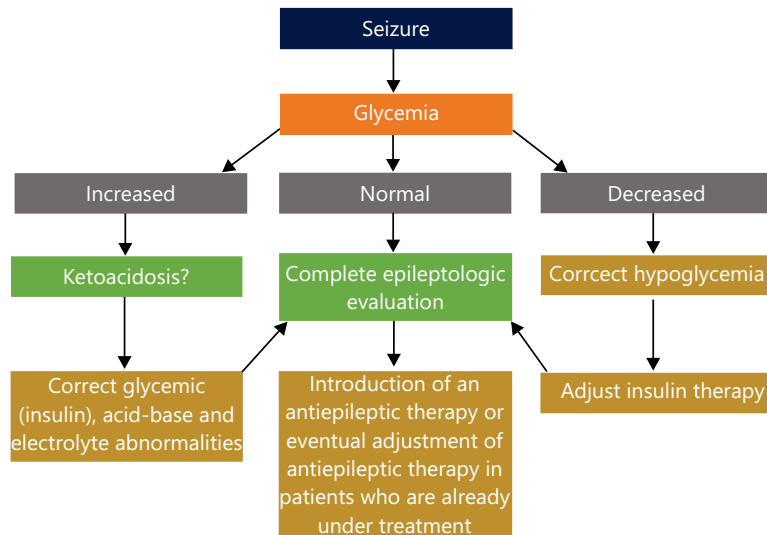


Fig. 1: Potential pathways for treating and managing patients

ketosis brought on by fasting and ketosis brought on by insulin shortage, the authors of these trials all stressed the significance of regularly monitoring insulin therapy and glucose levels²⁷. The following illustration (Fig. 1) below summarizes potential pathways of treating and managing these patients.

CONCLUSION

There is compelling evidence for a tight association between hyperglycemia and epilepsy. Individuals with epilepsy are at a higher risk of developing hyperglycemia due to the use of antiepileptic medications. The management of these conditions involves monitoring blood sugar levels and electrolytes regularly, making lifestyle changes to improve glycemic control and adjusting both anti-diabetic and anti-epileptic medications to minimize the risk of both hyperglycemia and seizures. By working closely with healthcare providers, people with epilepsy and hyperglycemia can manage their conditions effectively and improve their quality of life.

SIGNIFICANCE STATEMENT

Significant diseases that are becoming recognized to be related to one another are hyperglycemia and epilepsy. The increased frequency of epilepsy and DM together is highlighted by epidemiological statistics, underscoring the necessity for customized therapeutic approaches. Thus, this research investigates the intricate relationship between hyperglycemia and epilepsy. Also, explores the pathophysiology of neurotransmitter activity changes, electrolyte imbalances and effects on neuronal excitability that are brought on by hyperglycemia. Clinical problems develop when DM coexists with epilepsy because some antiepileptic drugs might affect glycemic management and vice versa. The review focuses on the age of onset, risk factors and possible comorbidities as it investigates the epidemiology of these coexisting diseases.

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