

Ketosis Based Therapy for Psychiatric Conditions

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ABSTRACT

Purpose: The ketogenic diet is a low carbohydrate, moderate protein, and high fat diet which results in a metabolic state known as ketosis, in which fats are broken down into ketone bodies. The ketogenic diet is a 100-year-old evidence-based treatment for epilepsy and is gaining popularity as a treatment for various mental disorders, including mood disorders.

Objective: to explain the potential mechanisms through which ketogenic diets may improve the pathophysiology of mood disorders and provide a comprehensive review of recent clinical literature on the topic Mood disorders are associated with mechanisms like mitochondrial dysfunction, oxidative stress, inflammation, and insulin resistance. The ketogenic diet addresses these underlying causes and may improve symptoms in people with mood disorders by potentially reducing the need for medications, and reduce common side effects and comorbidities, such as weight gain and insulin resistance.

KEYWORDS: Major depressive disorder, ketosis, Bipolar disorder, treatment resistant depression

INTRODUCTION

The ketogenic diet (KD) is a moderately protein-rich, low-carb, high-fat diet that has demonstrated promise in treating neurological conditions and may be a therapeutic alternative for those with psychiatric illnesses or mood disorders ^[1].

Ketogenic Diet: the following are the daily intake of Keto diet as shown in the figure 1

- **High fat:** Typically, 70-80% of the daily caloric intake comes from fats.
- **Low carbohydrate:** Carbohydrates are usually limited to 5-10% of daily intake, often around 20-50 grams of net carbs per day.
- **Moderate protein:** Protein makes up about 15-20% of the daily caloric intake, which helps prevent the body from

converting too much protein into glucose (gluconeogenesis).

Mood disorders, including depressive and bipolar disorders, are chronic and recurrent conditions that significantly impact emotions, energy, and motivation. These disorders affect millions globally, with major depressive disorder (MDD) affecting approximately 7% of adults in the U.S. annually, and bipolar disorder (BD) affecting 1.5-2.4% of the population ^[2]. Despite the availability of treatments like medication and psychotherapy, many individuals remain treatment-resistant, with an estimated 30% of people with MDD and bipolar depression not responding to standard therapies. This highlights the urgent need for new treatment options ^[3].

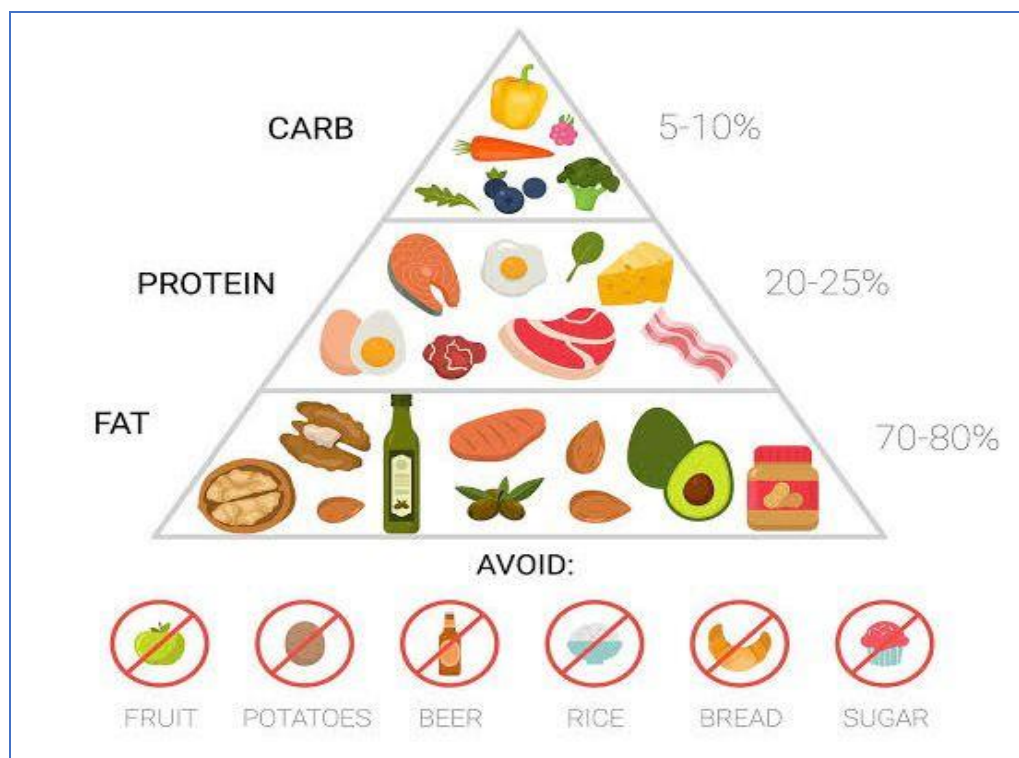


Figure 1: Keto Diet

Recent research has focused on metabolic therapies, such as the ketogenic diet, to improve symptoms and functional outcomes in mood disorders [4]. The ketogenic diet, characterized by high fat, moderate protein, and low carbohydrate intake, induces ketosis - a metabolic state where the body produces ketone bodies as an alternative energy source to glucose. Ketones help bypass steps in glucose metabolism, thereby reducing lactate accumulation and promoting energy production when glucose metabolism is impaired [5]. This diet has been used for over a century to treat epilepsy, and its role in mood disorders is gaining attention. The production of ketone bodies provides the brain with an alternate fuel source to glucose.

Evidence suggests the ketogenic diet may target underlying pathophysiologic mechanisms of mood disorders. In addition to reducing blood glucose and insulin levels, the diet has shown improving mood symptoms [6]. Interestingly, several anticonvulsant medications, which are used in epilepsy treatment, are also FDA-approved for bipolar disorder, highlighting a potential link between metabolic therapies

and mood regulation. Given the growing interest in metabolic treatments, this article aims to review clinical data on the ketogenic diet's potential as a therapeutic approach for mood disorders, specifically bipolar disorder. In this review, we hope to present data from randomized clinical trials, case series and new areas of research in recent years.

Therapeutic Benefits of ketogenic diet in Neurological Disorders:

In the 1920s, the ketogenic diet was first created to treat epilepsy, especially in individuals who did not react well to medicine. It is believed that the KD's function in neurology is related to its capacity to change the body's energy generation from glucose to ketones, which are created from the metabolism of fat, perhaps stabilizing brain function [7].

A significant issue for millions of individuals globally is the sharp and rapid rise in neurological illness incidence, especially neurodegenerative diseases.

role of the ketogenic diet in the therapy of neurological diseases such as: epilepsy, Alzheimer's disease (AD), Parkinson's

disease (PD), multiple sclerosis (MS) and migraine^[8].

- **Epilepsy:** The KD has a well-established track record of lowering seizure frequency and intensity in epileptic patients, particularly in kids who don't react to antiepileptic medications.
- **Alzheimer's Disease:** According to some research, the KD may help control Alzheimer's disease symptoms by giving the brain another energy source and lowering the production of amyloid plaque, which is linked to neurodegeneration.
- **Parkinson's Disease:** The advantages of KD for Parkinson's patients are still being investigated, especially with regard to neuroprotection and cognitive enhancement.
- **Migraine:** The KD stabilizes brain metabolism, which may help lower migraine frequency.

Potential Benefits in Psychiatric Disorders:

Newer studies indicate that the ketogenic diet might potentially help treat some mental illnesses, although more data is

required to draw firm conclusions. Some potential applications include:

- **Bipolar Disorder:** By modifying brain metabolism and neurotransmitter balance, the KD may reduce mood swings, however this is still being investigated^[9].
- **Schizophrenia:** Some studies suggest that the KD could help reduce symptoms of schizophrenia, possibly due to its effects on brain energy metabolism and neuroinflammation.
- **Depression:** Some research suggests that ketones themselves may have antidepressant properties, and the ketogenic diet may calm mood.
- **Anxiety and Stress:** Although research is still in its early stages, the KD may help to improve stress resilience and lessen anxiety by fostering a more reliable and effective brain energy supply^[10].

Mechanisms Behind KD's Effects:

Knowledge on the fundamental mechanisms of KD has steadily increased during the last 20 years. The figure 2 shows the importance of ketogenic diet in the treatment of neurological diseases.

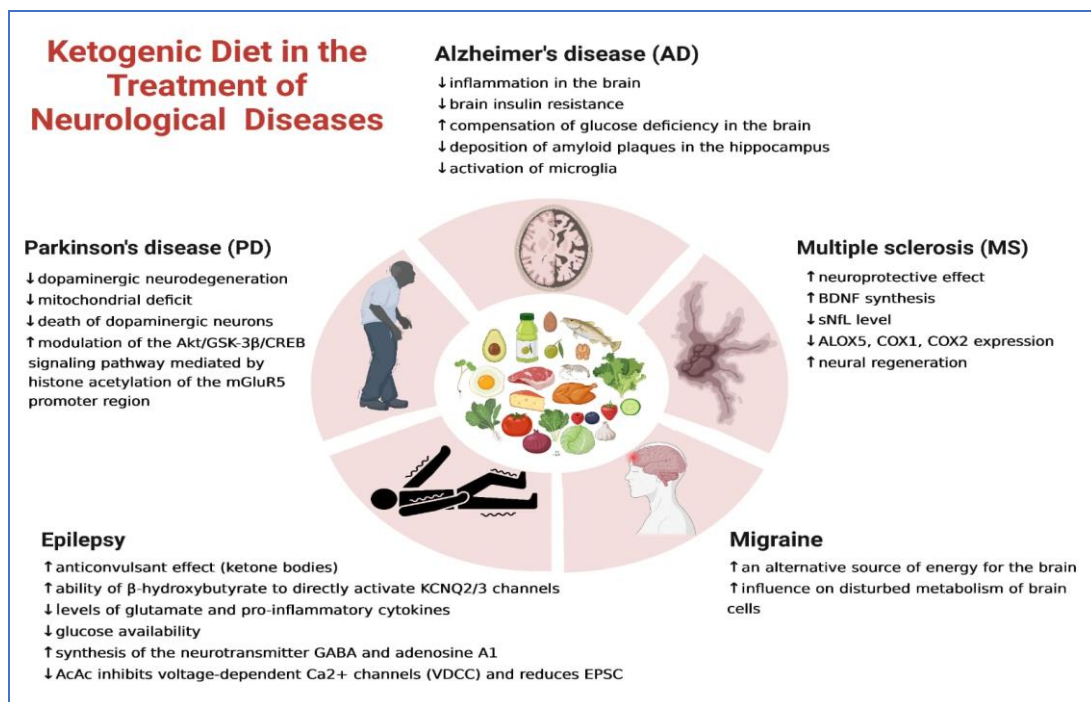


Figure: 2

Mitochondrial Dysfunction

Being essential cellular components, mitochondria are important for energy production as well as brain function, especially when it comes to energy production, neural activity, and cognitive flexibility. Evidence of energy dysregulation, including an imbalance in NAD⁺/NADH and a reduction in ATP production during periods of high demand, links mood disorders to mitochondrial dysfunction. influencing both short-term and long-term neural plasticity, controlling neuronal activity, enhancing cellular resilience, and promoting behavioral changes. Because the brain's store capacity is limited and its ATP expenditure is high.

The ketogenic diet is promoted as a potential treatment for mood disorders by increasing energy metabolism, lowering inflammation and oxidative stress, and promoting mitochondrial biogenesis. Ketone bodies, which are better for mitochondrial use, replace glucose as the body's primary energy source when following a diet, enhancing cellular resilience and health. According to research by Veech and associates, the ketogenic diet improves mitochondrial function^[11].

Inflammation

Numerous pieces of evidence point to links between mood disorders and inflammation. People with MDD and BD have higher levels of inflammatory markers, such as C-reactive protein, tumor necrosis factor (TNF) alpha, and the interleukins IL-1, IL-2, IL-6, and IL-10^[12,13].

There have been notable decreases in inflammatory biomarkers linked to the ketogenic diet. A systemic anti-inflammatory effect was suggested by Masood et al.'s meta-analysis, which emphasized the diet's effectiveness in lowering C-reactive protein, a crucial indicator of inflammation, across many investigations^[14].

GABAergic activity:

In humans, excitatory and inhibitory impulses are transmitted by glutamate and GABA neurons, respectively, and these signals work in concert to maintain optimal brain function. Research suggests that depression may be related to an imbalance between the inhibitory (like the GABA system) and excitatory (like the glutamatergic system) systems. According to some research, depression causes a disruption in GABAergic neurotransmission, and GABA concentrations are markedly lowered, particularly in TRD. An inhibitory neurotransmitter called GABA may be activated more by the KD, which can help calm neural activity^[15].

CONCLUSION

The ketogenic diet (KD) has gained attention as a potential therapeutic approach for various neurological and psychiatric disorders, including mood disorders like depression and bipolar disorder. By altering the body's energy metabolism from glucose to ketones, the KD offers an alternative energy source for the brain, which may help stabilize brain function and improve mood regulation. This dietary approach, which involves high fat, moderate protein, and low carbohydrate intake, has been shown to reduce blood glucose and insulin levels, promote mitochondrial health, and decrease inflammation factors, enhanced GABAergic activity all of which contribute to better brain health and resilience.

The KD's potential therapeutic effects in neurological conditions such as epilepsy, Alzheimer's disease, and Parkinson's disease are well-established, with research suggesting that it can stabilize brain metabolism and even reduce seizure frequency. For psychiatric disorders, the KD may have mood-stabilizing effects, with preliminary studies indicating its benefits in conditions like bipolar disorder, depression, anxiety, and schizophrenia, potentially due to its effects on brain metabolism, neurotransmitter balance, and inflammation.

Thus more research is needed to fully understand the KD's impact on psychiatric disorders, the diet's growing evidence suggests it may offer a promising alternative or adjunctive therapy for individuals with treatment-resistant mood disorders, marking an important step toward more effective management of these conditions.

Declaration by Authors

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