

The use of a low carbohydrate, ketogenic diet in bipolar disorder: systematic review

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Systematic Review

Keywords: Bipolar disorder, ketogenic diet, low carbohydrate high fat, metabolic health, metabolic dysfunction, obesity

Posted Date: March 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-334453/v1>

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Abstract

Background: Bipolar disorder is a neurodevelopmental illness characterized by severe biphasic changes in mood, energy, or thought. Key underlying metabolic pathologies thought to play a role include dysfunction in energy metabolism. The purpose of this article is to review the findings to date of the effects of a low carbohydrate ketogenic diet (KD) on mood symptoms in preclinical and clinical models of bipolar illness. The review highlights the underlying metabolic pathologies of bipolar disorder (BD) and potential therapeutic effects of the KD on these pathologies. The article also explores the potential effects of a KD on metabolic health in BD, including proposed mechanisms of action.

Summary: Recent findings support the idea that bipolar disorder, along with other psychiatric disease, may have roots of metabolic dysfunction: cerebral glucose hypometabolism, oxidative stress, as well as mitochondrial and neurotransmitter dysfunction which has downstream effects on synapse connections. A KD provides alternative fuel to the brain aside from glucose and is believed to contain beneficial neuroprotective effects, including stabilization of brain networks, reduction of inflammation and oxidative stress. Several beneficial metabolic effects on insulin resistance, weight, and lipids have been shown. Based on its effectiveness in treating epilepsy, the KD has garnered recent interest in its application for mood disorders as it may imitate the pharmacological effects of mood stabilizers, commonly prescribed agents in the treatment of both BD and epilepsy. Additionally, it may improve metabolic dysfunction often seen in BD and repair deficits in energy metabolism. Limited case studies on KD treatment in BD have been reported; however, studies addressing the potential therapeutic effects of KD on metabolic abnormalities in mental illness are promising. Literature of plausible mechanisms and reports of improvements in psychosis, cognition and mood symptoms have been increasing.

Conclusions: Preliminary findings support further testing of a low carbohydrate KD as a potential therapeutic tool in repairing energy metabolism in bipolar illness. Further research and clinical trials are needed to evaluate the efficacy of a KD as a supplemental or co-treatment of bipolar illness and the first open-label trial testing the diet in bipolar illness is currently underway at Stanford.

Background

Bipolar disorder (BD) is a serious, multidimensional neurodevelopmental illness characterized by severe biphasic changes in mood, energy, and thought which impairs functional ability. This illness affects approximately 9.2 million (2.8%) adults in the United States every year, is the 17th leading cause of global burden of disease and has the highest suicide rate among affective disorders (Gonda et al., 2012; Harvard Medical School; National Institute of Mental Health; Vigo, Thornicroft, & Atun, 2016). The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association) classifies BD into four categories according to the severity of manic and depressive episodes: bipolar I disorder, bipolar II disorder, cyclothymia, and atypical. Symptoms during a manic episode can include grandiosity, elevated energy levels, decreased need for sleep and heightened emotional expressions. Objective indicators of a depressive episode include changes in appetite, feelings of worthlessness,

fatigue, and frequent suicidal thoughts. Due to its recurrent and cyclical nature, continuous treatment of BD is often necessary and involves a combination of medication and psychotherapy. Pharmacological agents used in managing symptoms include mood stabilizers and antipsychotics that act primarily on sodium channels, dopamine D₂ and serotonergic 5-HT₂ receptor targets (Arranz, Salazar, & Hernandez, 2021; Himmerich & Hamilton, 2020; Sadek, 2021). With addressing these primary mechanistic targets, unwanted adverse metabolic side effects, such as weight gain, or other neurological, cardiovascular, effects can occur. (Arranz, Salazar, & Hernandez, 2021; Himmerich & Hamilton, 2020).

Increased understanding of the metabolic and biological pathways in BD has shifted some research focus on alternative nutritional interventions (Brietzke et al., 2011; Mansur et al., 2015; Sayuri, Yamagata et al., 2017). Although research has been limited, diet is acknowledged to influence several biological processes, including mitochondrial activity, immune/inflammatory processes, oxidative stress, monoaminergic activity, and neuroprogression (Lopresti & Jacka, 2015). Recently, studies have investigated the ketogenic diet (KD) as a potential treatment for neurodegenerative and neuropsychiatric conditions (Brietzke et al., 2018; Kraeuter, Phillips, & Sarnyai, 2020; McDonald & Cervenka, 2018). This high-fat, moderate protein, low-carbohydrate diet releases ketone bodies from the breakdown of fat and serves as an alternative fuel, diverting away from the use of glucose as the body's main energy source. A KD has been shown to have beneficial effects on metabolic health, such as improving blood glucose, body weight, insulin resistance, triglycerides, and cholesterol (Cantello et al., 2007; Cunnane et al., 2002; Dashti et al., 2004; Sumithran et al., 2013; Thio et al., 2006; Yudkoff et al., 2001) which may counteract the effects of metabolic abnormalities seen in with psychotropic medication use. Furthermore, the change in metabolic processes seen in a KD may have antidepressant and mood stabilizing effects, making it a promising treatment intervention in bipolar disorder (Murphy et al., 2004). This review aims to summarize the current preclinical and clinical evidence on the effects of a KD and discuss its potential application as a supplemental non-pharmacological intervention for BD as well as in treatment of metabolic dysfunction often seen with antipsychotic medications.

I. Mechanisms And Pathophysiology Of B D

Several biological mechanisms have been proposed as potential underlying causes of BD. These include mitochondrial dysfunction (Jeong et al., 2020; Kato, 2017; Scaini et al., 2021; Scaini et al., 2016), oxidative stress (Knorr et al., 2019; Steullet et al., 2018), and neurotransmitter disruption (Liu, Zhao, & Guo, 2018; Martino & Magioncalda, 2021). Increasing numbers of genetic, biological, and neuroimaging studies have begun to address these hypotheses in recent years. When there is a dysfunctional biological mechanism, energy metabolism, cellular signaling, and circadian rhythms are some of the major processes shown to be impacted (Table 1).

A. Mitochondrial Dysfunction

Mitochondrial dysfunction has been identified as a potential precursor to BD. Mitochondria play a vital role in energy production, intracellular calcium (Ca^{2+}) regulation, synaptic plasticity, and reactive oxidative species (ROS) protection (Quiroz et al., 2008). Magnetic resonance studies have shown abnormal metabolism within the brain characterized by changes in aspartate, glutamate, choline, myo-inositol, lactate, phosphocreatine, phosphomonoesters, and intracellular pH which affects cell signaling (Stork & Renshaw, 2005). Biochemical and genetic data further supports the mitochondrial dysfunction hypothesis and its role in BD (Kato & Kato, 2000; Kim et al., 2017; Young, 2007).

1. Loss of Na^+/K^+ -ATPase Function

Mitochondrial dysfunction can impact the energy requirements for neural processes. Inability to regulate Ca^{2+} concentrations can impact energy production (Kim et al., 2017). Loss of Na^+/K^+ -ATPase function leads to elevated levels of Ca^{2+} and decreased levels of ATP (Silver, Deas, & Erecińska, 1997). Slight decreases in ATP levels can change the duration of neurotransmitter release and cause neurons to enter either the excitatory or refractory states (El-Mallakh & Wyatt, 1995). Thus, the manic and depressed states of BD could be influenced by a change in the threshold needed for neuronal activation (El-Mallakh & Wyatt, 1995). Normal ATP levels can only be achieved through both oxidative phosphorylation and glycolysis, so it is likely that a reduction of Na^+/K^+ -ATPase function leads to the impairment of oxidative phosphorylation (Silver, Deas, & Erecińska, 1997). However, the mechanism of dysfunction in oxidative phosphorylation is currently unknown (Campbell & Campbell, 2019). The bulk of ATP is produced via the final stage of cellular respiration; thus, a loss of function in vital proteins can potentially lead to a significant decrease in ATP levels.

2. Pyruvate Dehydrogenase Complex Dysfunction

A decrease in sustainable energy levels could alter brain function. Disruption in the ATP production pathway between glycolysis, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation has been hypothesized to play a role in BD (Campbell & Campbell, 2019). Pyruvate is produced at the end of glycolysis and converted into acetyl-CoA to be used in the TCA cycle. The pyruvate dehydrogenase complex (PDC) is responsible for this conversion. Elevated levels of pyruvate have been observed in BD, indicating a disruption in the PDC (Yoshimi et al., 2016). Lactate, a byproduct of glycolysis, is another biomarker shown to increase in BD (Regenold et al., 2009). Impairment of the enzyme could shift the primary energy production method to glycolysis only and disrupt oxidative phosphorylation (Campbell &

Campbell, 2019). As sustainable levels of ATP cannot be produced by glycolysis only, dysfunction of the PDC is likely to have downstream effects on neuronal activity that influences mood states in BD.

B. Oxidative Stress

Long-term oxidative stress can cause irreversible damage to the neural system. Recent studies increasingly offer evidence to support oxidative stress as an underlying mechanism of BD (Jimenez-Fernandez et al., 2020; Kim et al., 2017; Scaini et al., 2016). ROS are a natural byproduct of energy metabolism and cell function. The bulk of free radicals are produced during oxidative phosphorylation and are neutralized through a series of biochemical pathways (Adam-Vizi & Chinopoulos, 2006). Failure to eliminate ROS can result in oxidative stress and cellular damage (Halliwell, 2007). Meta-analysis studies have shown significant increase in selective ROS in patients with BD (Andreazza et al., 2008; Brown, Andreazza, & Young, et al., 2014). However, the availability of experimental data is limited. Trials with antioxidant treatments have also shown contradictory results, suggesting that oxidative stress may be influenced by mitochondrial dysfunction (Kim et al., 2017). Whether it is a primary or a secondary pathomechanism, chronic cellular damage is likely to cause gaps within neurotransmission and potentially manifest as symptoms seen in BD.

C. Monoaminergic Activity

Dysfunction in neurotransmitter pathways has been hypothesized to be a possible biological mechanism of mood disorders, including BD. The central nervous system (CNS) relies on tightly regulated monoaminergic activity; an imbalance in concentrations can affect behavior and emotion (Wang et al., 2020). Antidepressants commonly target and regulate these monoaminergic circuits, supporting a significant role of monoamines in the cycles of depression and mania (Van Bockstaele, 2013). Dopamine, γ -aminobutyric acid (GABA), glutamate, norepinephrine, and serotonin (5-HT) pathways have been shown to influence mood and mood regulation (Manji et al., 2003; Sigitova et al., 2017).

1. Dopamine, Serotonin, and Norepinephrine Pathways

Altered levels of neurotransmitters that regulate mood, emotion, and cognition can affect neural processes. Dopamine plays a role in arousal, reward, and motivation and influences mood. Functional failure in dopamine receptors and transporters has been speculated to be an underlying cause of BD (Ashok et al., 2017). Excessive dopamine activation with continuous stimulation of neurons can lead to

manic symptoms (Berk et al., 2007). The neurotransmitter's ability to increase dopaminergic activity can consequently cause oxidative stress (Rees et al., 2007). Mood is also affected by serotonin, which regulates metabolism, emotion, and cognition. Alterations in 5-HT levels could contribute to the depressive episodes of BD (Mann et al., 1996). Patients with BD have been reported to have lower 5-HT activity (Mahmood & Silverstone, 2001). Both human and animal studies have also shown significant associations between reduced serotonin receptors and BD (Sobczak et al., 2002; Rao et al., 2019). Norepinephrine is another neurotransmitter that plays a role in regulating cognition, motivation, and intellect. Evidence suggests that a decrease in norepinephrine levels and lower activation of noradrenergic pathways induces depression and depressive symptoms (Moret & Briley, 2011; Stahl, 2013). Since BD is a mood disorder, a disruption in the neurobiochemical pathways influencing mood and emotion can potentially be an underlying pathophysiology.

2. GABA and Glutamate Pathways

Neural function depends on a balanced cycle of inhibitory and excitatory neurotransmitters. GABA and glutamate both balance the glutamatergic system, where changes in the levels of either molecule could induce depressive symptoms. Excessive stimulation of glutamatergic receptors and accumulation of glutamate could cause neuronal death (Wang & Qin, 2010). Numerous magnetic resonance spectroscopy studies showed an increase in glutamate levels in frontal brain areas within adult BD patients (Ehrlich et al., 2015; Gigante et al., 2012). Higher levels of glutamatergic function may also impact energy requirements. Glycolysis has been observed to increase in patients with BD, where most of the energy produced in the cortex has been suggested to support GABA and glutamate signaling pathways (Dager et al., 2004; Sibson et al., 1998). Constant energy production via glycolysis is unsustainable and chronic stimulation can be detrimental to cellular receptors, likely impacting neuronal function downstream and contributing to the symptoms seen in BD.

D. Glycogen Synthase Kinase-3 (GSK-3) Enzyme

Neuronal damage due to an imbalance in neuroprotective enzymes could be another potential underlying cause of BD. GSK-3 is an essential enzyme for cellular signaling and plays an important role in regulating apoptosis (Gould, Zarate, & Manji, 2004). Studies have shown increased apoptosis in neuronal cells with increasing GSK-3 activity and decreased cell apoptosis with decreasing GSK-3 activity (Hetman et al., 2000; Maggirwar et al., 1999; Pap & Cooper, 1998). Cell death and neuronal damage could create gaps in signaling pathways that would detrimentally affect functional ability. Evidence has also suggested GSK-3 may regulate the circadian cycle (Kaladchibachi et al., 2007). Disrupted circadian responses are known to be associated with mood disorders (Walker et al., 2020). Additionally, GSK-3 has recently been

hypothesized to be a common etiology between patients whose longitudinal diagnoses progressed negatively from depression to BD to dementia (Terao, Ishii, & Hirakawa, 2020). The potential role of GSK-3 dysfunction in the negative progression of BD due to increase in neuronal cellular apoptosis further emphasizes the importance of shielding against neuronal damage.

| Table 1. Potential effects of a KD on proposed biological mechanisms of BD | | |
|---|---|---|
| BD Mechanisms | BD Symptoms | Potential KD Effects |
| <i>Mitochondrial Dysfunction</i> | Decrease in energy level production | Induces mitochondrial biogenesis |
| <i>Na/K ATPase Loss of Function</i> | Impaired ATP production via oxidative phosphorylation | Provides alternative energy production pathway via ketosis |
| <i>PDC Dysfunction</i> | Unsustainable ATP levels due to glycolysis-only production | Provides alternative energy production pathway via ketosis |
| <i>Oxidative Stress</i> | Increase in ROS leading to neuronal damage | Reduces ROS levels with ketone bodies; Increases HDL cholesterol levels for neuroprotection |
| <i>Monoaminergic Activity</i> | Changes in behavior and emotion due to imbalance neurotransmitter concentrations | Regulates neurotransmitter metabolites via ketone bodies and intermediates |
| <i>Dopamine</i> | Increase in receptor activation inducing mania symptoms | Decreases dopamine metabolites |
| <i>Serotonin</i> | Reduced levels inducing depressive symptoms | Decreases serotonin metabolites |
| <i>Norepinephrine</i> | Reduced levels inducing depressive symptoms | No significant changes observed in prior studies |
| <i>GABA</i> | Reduced levels related to depressive and mania symptoms | Increases GABA levels |
| <i>Glutamate</i> | Increase in levels leading to unsustainable energy requirements and neuronal damage | Decreases glutamate levels |
| <i>GSK-3 Enzyme Dysfunction / Deficiency</i> | Apoptosis and neuronal damage | Increases antioxidants to provide neuroprotection |

2. K D As A Treatment For B D

The ketogenic diet has been used as an effective intervention for epilepsy since the 1920s (Neal et al., 2008). Recently, it has garnered more interest on its potential therapeutic effects on neuropsychiatric disorders and BD (Dsouza, Haque & Aggarwal, 2019; El-Mallakh & Paskitti, 2001). The nutritional plan use fats as its main energy substrates replacing glucose by reducing carbohydrate intake. Under ketogenesis, fat is converted into fatty acids and ketone bodies. The ketone bodies can be directly transported to the brain and inserted into the TCA cycle to produce ATP (Masood, Annamaraju, & Uppaluri, 2020). Alternatively, the ketones can be converted into glucose via gluconeogenesis that can then enter glycolysis (Masood, Annamaraju, & Uppaluri, 2020). The ability to switch the body's main energy source from sugars to fats by leveraging alternative metabolic pathways makes KD a promising treatment to target the energy deficiencies of BD.

A KD can potentially imitate the pharmacological effects of mood stabilizers. Mood stabilizers are the most prescribed types of pharmacological agents for acute treatment of BD. The three broad categories of mood stabilizers used are lithium salts, anticonvulsants, and antipsychotics (Gelenberg & Hopkins, 1996; Grunze, 2010; Malhi et al, 2013). The clinical efficacy of these medications varies with the type of BD and much of their biochemical mechanisms remain unknown (Leo & Narendran, 1999). Adverse side effects can occur with long-term use of pharmaceuticals, often resulting in chronic cardiovascular and metabolic impacts (Dols et al., 2013; Geddes & Miklowitz, 2013). Investigating the use of KD as a clinical treatment is worthwhile since it can potentially circumvent detrimental side effects and manage symptoms of BD (Table 1).

A. KD and Energy Metabolism

KD can potentially bypass or restore mitochondrial function by providing alternative pathways toward energy metabolism, targeting one of the top hypothesized mechanisms of BD. Animal and human model studies have reported an increase in mitochondrial biogenesis, an increase in mitochondrial mass, and an increase in energy production after treatment with KD (Hasan-Olive et al., 2019; Hubbard, Vekaria, & Sullivan, 2021). Measuring the mitochondrial activity within the rat hippocampus revealed that rats who achieved chronic ketosis had an increase in mitochondrial proteins and genes encoding for oxidative phosphorylation (Bough et al., 2006). Hippocampal slices from KD-fed rats were more resistant to metabolic stress than control rats, suggesting that mitochondrial biogenesis has occurred to a level that can sustain increased metabolic need (Bough et al., 2006). Treatment of cultured human fibroblasts, mice hippocampal neurons, and rat hippocampal neurons with ketone bodies showed an improvement of markers for mitochondrial function (Hasan-Olive et al., 2019). There was also an increase in oxygen consumption rate and NAD^+/NADH ratio—an essential parameter indicative of improved and more efficient cellular respiration (Hasan-Olive et al., 2019). Ketosis is also thought to alter extracellular and

intracellular ion concentrations, mimicking the therapeutic effects seen with mood stabilizers (El-Mallakh & Paskitti, 2001).

KDs has also been studied on patients with PDC deficiency, but studies have yet to be conducted on patients with PDC dysfunction. As early as the 1970s, ketosis has been observed to decrease blood pyruvate levels and dampen the severity of neurodegeneration in pediatric patients with PDC deficiency (Falk et al., 1976). Varying degrees of a carbohydrate restrictive diet also improved neurological conditions for seven patients with genetic mutations to the PDC (Wexler et al., 1997). Although KD is not enough to completely reverse the neurodegenerative effects of PDC, early intervention with the diet may prevent future damage from PDC deficiency (Wexler et al., 1997). A recent study evaluated the long-term efficacy and safety of KD in nineteen pediatric patients with PDC deficiency (Sofou et al., 2017). Almost all patients showed some degree of improvement across motor, cognitive, social, and epilepsy measures. Lactate levels significantly decreased after KD initiation, indicating ketone bodies bypassed glycolysis and directly entered the TCA cycle. While minor side effects were observed in some of the patients such as episodic ataxia and slight cognitive decline, they were attributed to underlying health conditions and non-compliance with KD and were not considered detrimental (Sofou et al., 2017).

These studies demonstrated that the effects of KD were the most prominent when the patient was introduced to the diet early in their diagnosis. In one study, chronic ketosis, the ability to achieve and maintain nutritional ketosis over a six-month period, was needed to achieve long-term metabolic benefits. (Sofou et al., 2017). While the exact biochemical mechanisms of ketone bodies require more investigation, their role in supplementing energy metabolites and restoring partial mitochondrial function makes KD a strong potential treatment intervention for BD.

B. KD and Neuroprotection

Ketone bodies could play a role as antioxidants to counter the accumulation of ROS that could contribute to neuronal damage and BD symptoms. Animal studies have investigated the neuroprotective effects of KD. Mice fed for 10-12 days on KD showed an increase in mitochondrial uncoupling protein activity and a decrease in ROS (Sullivan et al., 2004). Two types of ketones— β -hydroxybutyrate and acetoacetate—were found to reduce ROS levels in isolated neocortical mitochondria (Maalouf et al., 2007). In a follow-up study, the ketone bodies were shown to prevent oxidative injury from hydrogen peroxide to neocortical slices of the rat brain (Kim et al., 2007). The neuroprotective benefits of KD are further observed in a study where rats were induced with a traumatic brain injury to increase production of ROS (Greco et al., 2016). Rats fed with KD after the injury showed a reduction in oxidative stress that was attenuated by ketones

(Greco et al., 2016). Key regulators of oxidative stress increased after KD treatment and anti-inflammatory effects were exhibited through the inhibition of inflammation-related signaling pathways (Lu et al., 2018). On the contrary, a randomized controlled study in healthy teenage athletes with a limited 3-week time frame showed that KD did not decrease ROS levels but did affect body composition (Rhyu, Cho, & Roh, 2014) and showed a significant increase in levels of HDL cholesterol compared to the non-KD group, indicating that the products of ketosis might be acting as antioxidants by impacting cholesterol ratios instead of affecting ROS levels (Rhyu, Cho, & Roh, 2014). Further investigation is required to determine specific mechanisms of a KD on oxidative stress through influences on ROS and antioxidant levels. It is likely that the anti-inflammatory effects of ketone bodies are achieved by affecting multiple biochemical pathways. As the pathophysiology of BD may involve numerous mechanisms, KD can potentially buffer against multiple causes of oxidative stress.

C. KD, Neurotransmitters, and Neurotransmission Pathways

Intermediates from ketosis might have a role in attenuating the manic and depressive symptoms potentially caused by disruptions in neural pathways by regulating neurotransmitters. Evidence of elevated GABA levels was found within the forebrain of KD-treated mice (Daikhin & Yudkoff, 1998). The process of converting ketone bodies into acetyl-CoA was suspected to free up glutamate used as part of TCA to be used for the synthesis of GABA (Daikhin & Yudkoff, 1998). Elevated glutamate and glutamine levels were also found within the hippocampus of KD-treated rats (Bough et al., 2006). Glutamate used within neurons are not obtained from blood and must be synthesized within the brain. Synthesis is an energetically demanding process; thus, any changes to normal energy levels could decrease production of glutamate. The mechanism of ketosis is thought to favor the release of glutamate from the nervous system, as decreasing glutamate levels have been associated with decreasing glucose levels and increasing GABA levels (Calderon, Betancourt, Hernandez, & Rada, 2017; Yudkoff et al., 2004). Although the exact mechanisms of KD on glutamate and GABA remains to be determined, it is hypothesized that KD can alter the dynamics of the glutamatergic cycle (Yudkoff et al., 2008).

Ketosis has also been observed to alter other neurotransmitter levels. No changes were measured in norepinephrine, dopamine, or 5-HT metabolites in rats treated for three weeks on KD regimen (Church, Adams, & Wyss, 2014). However, there was a significant increase in cortical dopaminergic activity, suggesting that KD influences neurotransmitter activity rather than concentration (Church, Adams, & Wyss, 2014). Neurotransmitter metabolites were also examined in human trials. After the 3-month KD treatment, dopamine and serotonin metabolites decreased in pediatric patients with epilepsy, but no changes in norepinephrine metabolites were observed (Dahlin, Mansson, & Amark, 2012). Future research

is needed to understand the specific mechanistic effects of KD on monoaminergic activity. However, existing evidence supports the impact of ketosis in regulating neurotransmission that may be beneficial in addressing the mood symptoms of BD.

D. KD, Metabolic Health, and Mood

BD is known to have higher comorbidity with several chronic metabolic diseases, such as obesity, type 2 diabetes, and cardiovascular disease (Perugi et al., 2015). Nutritional ketosis has been associated with large scale beneficial effects on metabolic health (Miller, Villamena, & Volek, 2018). For example, participants assigned a low-carbohydrate KD in a randomized controlled trial reported significant decreases in body mass index (BMI) after six months, along with improvements in mood and hunger. (McClernon et al., 2007). Similarly, participants in an uncontrolled intervention study had experienced a decrease in insulin levels, BMI, and cognitive functions after 12 weeks (Mohorko et al., 2019). Improvements in metabolic profile with KD have also been characterized by decreasing levels of triglycerides and low-density lipoprotein cholesterol (LDL) and increasing levels of high-density lipoprotein (HDL) cholesterol (Dashti et al., 2006; Yancy et al., 2004). An open-label, non-randomized, controlled study had recently demonstrated improved lipid-lipoprotein profiles and glycemic control in patients with Type 2 diabetes treated with KD (Hallberg et al, 2018). A limitation within these studies is the lack of documentation of the psychiatric diagnosis at baseline enrollment; nevertheless, the evidence supporting the metabolic effects of a KD further adds to the potential as a supplemental treatment in BD.

E. KD as a Treatment Intervention for BD

Although KD is currently being investigated as a treatment for metabolic and neurological disorders, the availability of clinical human data on KD in BD is limited to two prior case studies. The first case series focuses on two female patients with bipolar II disorder who were prescribed a KD and maintained nutritional ketosis for up to 3 years (Phelps, Siemers, & El-Mallakh, 2013). Both patients achieved mood stabilization comparable to the effects typically experienced with medication, and neither experienced adverse effects from KD (Phelps, Siemers, & El-Mallakh, 2013). It was hypothesized that a KD reduced intracellular sodium and calcium, which acidified blood plasma and stabilized mood (Phelps, Siemers, & El-Mallakh, 2013). The second case study involved a patient with early onset BD, who did not show improvement of symptoms however a lack of urinary ketosis was found after a month-long treatment, suggesting that ketosis was not actually achieved (Yaroslavsky, Stahl, & Belmaker, 2002). Adverse side effects were absent. In addition to the case studies, a recent observational analytic study summarized positive self-reported effects of the ketogenic diet from members of online bipolar disorder forums (Campbell & Campbell, 2019). Significant mood stabilization, improved clarity of thought, increased

energy, and weight loss were some of the positive impacts reported; no adverse side effects were reported. Due to these limited findings, it is not possible to draw conclusions on the overall effects of a KD in this population.

3. Discussion

This review outlines the metabolic, neuroprotective, and neurochemical benefits of KD and its potential to target the biological mechanisms of BD. Little research is available on the effects of the diet on mood disorders, compared to the robust evidence currently supporting KD as an established treatment for epilepsy. While animal models have been reliable in assessing the potential implications and safety of the dietary intervention, there is a gap in our understanding of its effects on human patients with BD.

Limitations

Several challenges are anticipated in future KD studies. Ketosis might not be achieved, either due to patient non-compliance or length of study. Mimicking the biochemical effects of KD by administering ketone bodies or intermediate substrates could circumvent this limitation, however exogenous versus endogenous production may result in varied outcomes. Regular measures of blood ketosis biomarkers can also be used to confirm patient compliance over long-term studies. As metabolic change from diet is not an instantaneous process, extending treatment periods beyond a few months is recommended to allow for adequate body adjustment. Inconsistent dietary plans also affect biological measures. Although preserving the high-fat and low-carbohydrate regimen, current studies on KD prescribed various percentages of carbohydrates that ranged from low to none (Bueno et al., 2013; Dashti et al., 2006; Yancy et al., 2004). A standardized nutritional formula will contribute to treatment consistency and improve validity of measurable outcomes. Additionally, differences in patient biological profiles and severity of BD symptoms can affect outcomes seen on a KD. Enrolling patients with similar illness severities could minimize confounders to better evaluate the efficacy of the treatment.

Future Work

Currently available KD research does not address the biochemical and metabolic effects of KD on human patients with BD. Animal models cannot adequately depict the cyclic cycles of mania and depression of BD (Beyer & Freund, 2017). Although the pathophysiology of BD is not clearly understood, evidence from numerous studies supports the idea that impaired energy metabolism plays a vital role in the manifestation of symptoms. Nevertheless, results from prior KD studies show promise for its potential therapeutic properties in addressing this impairment. The mechanistic impact of the diet on BD remains

unknown and warrants further investigation. Open label trials and randomly controlled clinical studies would be the necessary next step to evaluate the efficacy of the nutritional intervention. To address this gap in knowledge, we are currently conducting a pilot open label clinical trial to investigate the effects of a low-carbohydrate, high-fat ketogenic dietary intervention in patients with BD and related metabolic comorbidities in the Metabolic Psychiatry Clinic at Stanford University School of Medicine. (<https://clinicaltrials.gov/ct2/show/NCT03935854>). The findings from the preliminary study will contribute guidance on future efforts to study the application of KD as a non-pharmaceutical treatment for BD.

4. Conclusion

A low carbohydrate, high-fat or KD diet has preliminarily been shown to beneficially modulate mood, behavior, and cognition, thus serves as a promising non-pharmacological treatment for BD that warrants further study. Supporting data from animal studies and preliminary findings from human models suggests that a KD may have therapeutic effects on psychiatric symptoms in addition to metabolic health. However, the efficacy of KD in patients with BD remains unproven due to the lack of open label and randomized controlled trials to date. Additional clinical research is necessary to further investigate the efficacy of a KD and its ensuing effects of ketosis in facilitating energy production, neuronal signaling pathways, and cellular protection.

List Of Abbreviations

5-HT: Serotonin

BD: Bipolar Disorder

BMI: Body Mass Index

GABA: γ -aminobutyric Acid

GSK-3: Glycogen Synthase Kinase-3

HDL: High-Density Lipoprotein

KD: Ketogenic Diet

LDL: Low-Density Lipoprotein

PDC: Pyruvate Dehydrogenase Complex

ROS: Reactive Oxidative Species

TCA: Tricarboxylic Acid

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: Not applicable

Competing Interests: The authors declare that they have no competing interests.

Funding: This work was not supported by any extramural funding.

Author Contributions: SSD developed the outline of the study and study procedures. BJY further refined the outline, conducted literature searches, reviewed papers, conducted analysis, and drafted the manuscript. RO contributed to the literature search process. All authors reviewed, revised, and approved the final manuscript.

Acknowledgements: Thank you to Sebastian Deri for reviewing the manuscript. Additionally, all authors would like to thank those struggling with mental illness who are helping contribute to advancement of metabolic psychiatry.

Authors' Information (Optional): Not Applicable

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