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The Ketogenic Diet in Depression: Potential Biological Mechanisms and Current Clinical Evidence - A Narrative Review

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Abstract

Background: Depression is a multifactorial psychiatric disorder whose underlying mechanisms extend beyond classical neurotransmitter abnormalities and involve metabolic, inflammatory and neurobiological disturbances. Recent evidence suggests that the pathophysiology of depression involves neuroinflammation, mitochondrial dysfunction, oxidative stress, neurotransmitter dysregulation and alterations in the gut–brain axis. These findings have contributed to growing interest in the field of metabolic psychiatry.

Aim: The aim of this review was to summarize the current evidence regarding the potential effects of the ketogenic diet on depressive symptoms and to discuss the biological mechanisms that may underlie these effects.

Material and methods: A literature was conducted using PubMed and Google Scholar. The review was based primarily on systematic reviews, meta-analyses, clinical trials, case reports and experimental studies addressing depression, ketogenic diet and metabolic psychiatry.

Results: The available evidence suggests that the ketogenic diet may contribute to the alleviation of depressive symptoms through the reduction of neuroinflammation and oxidative stress, improvement of mitochondrial function, modulation of neurotransmitter systems and regulation of the gut–brain axis. Preliminary clinical studies have reported improvements in depressive symptoms among patients following ketogenic interventions. However, the available studies are limited by small sample sizes and short follow-up periods.

Conclusions: The ketogenic diet may represent a promising adjunctive intervention for the management of depressive symptoms. Nevertheless, the current evidence remains insufficient to recommend it as a standard treatment for depression. Further large-scale, long-term randomized controlled trials are required to establish its efficacy and safety in patients with depressive disorders.

Key words: ketogenic diet; depression; metabolic psychiatry; neuroinflammation; mitochondrial dysfunction; oxidative stress

Introduction

Depressive disorders represent a major challenge in contemporary mental health care. As part of the broader group of neuropsychiatric disorders, they are associated with substantial impairment in daily functioning, reduced quality of life and a decrease in life expectancy of approximately 7–9 years [1]. Major depressive disorder (MDD) is characterized by a range of emotional, cognitive and somatic symptoms, with persistent low mood and anhedonia being among its core clinical features [2]. Despite the availability of pharmacological and psychotherapeutic interventions, approximately 30% of patients exhibit treatment resistance [1,3]. Furthermore, many individuals experience adverse effects of treatment and frequent relapses, highlighting the urgent need for the development of novel therapeutic approaches [1,2].

Increasing evidence indicates that mitochondrial dysfunction, chronic inflammation, oxidative stress and impaired brain glucose metabolism may contribute to the pathophysiology of depression [1,4,5]. These observations have led to the emergence of the concept of metabolic psychiatry, a rapidly developing field that investigates the relationship between metabolic processes and brain function [5,6].

Among the various metabolic interventions currently under investigation, nutritional approaches have attracted considerable attention. In particular, the ketogenic diet (KD) has emerged as a promising therapeutic approach [5]. The ketogenic diet is characterized by a substantial reduction in carbohydrate intake, increased consumption of fats and moderate protein intake, resulting in a metabolic state known as ketosis. During ketosis, the body

produces ketone bodies, which serve as an alternative and efficient energy substrate for the brain and may exert neuroprotective effects while promoting neuronal stability [1,7,8].

The aim of this review is to summarize the current evidence regarding the effects of the ketogenic diet on depressive symptoms and to discuss the potential biological mechanisms underlying these effects.

Ketogenic Diet: Definition and Physiological Basis

The ketogenic diet is characterized by a substantial reduction in carbohydrate intake (typically 20–50 g/day), increased fat consumption and moderate protein intake [9,10]. Due to the restricted availability of carbohydrates, the body gradually depletes glycogen stores in the liver and muscles and shifts its metabolism toward increased fatty acid oxidation [9, 11, 12]. Fatty acids are transported to the liver, where they are converted into ketone bodies through the process of ketogenesis [9, 12, 13].

Three major ketone bodies are produced during ketosis: acetone, acetoacetate, and β -hydroxybutyrate (BHB) [8,9]. These molecules serve not only as alternative energy substrates but also as signaling molecules involved in the regulation of multiple cellular pathways [1,12].

Under normal physiological conditions, glucose is the primary energy source for the brain, as fatty acids are unable to efficiently cross the blood–brain barrier [8,9]. In contrast, ketone bodies can readily enter the brain and, when present at sufficient concentrations, can provide a substantial proportion of its energy requirements [9, 14]. Ketone bodies may improve mitochondrial energy efficiency and ATP production while simultaneously reducing oxidative stress, thereby exerting neuroprotective effects [7, 12].

The ketogenic diet also lowers blood glucose and insulin levels, reduces markers of systemic inflammation and enhances mitochondrial function by providing an alternative energy substrate [1, 5, 7]. Ketosis has additionally been associated with increased mitochondrial biogenesis and improved cellular energy metabolism [1, 13, 15]. Furthermore, the ketogenic diet may influence neurotransmission by increasing γ -aminobutyric acid (GABA) activity and reducing

glutamatergic signaling, thereby contributing to the restoration of the excitatory–inhibitory balance within the central nervous system [1, 13, 14].

Pathophysiology of Depression

Depression is increasingly recognized as a multifactorial disorder involving complex interactions between inflammatory, metabolic, and neurobiological processes rather than solely alterations in neurotransmission [5, 16, 17].

One of the proposed mechanisms underlying depression is neuroinflammation, characterized by a chronic low-grade inflammatory state that activates the brain's immune cells, known as microglia, resulting in increased production of pro-inflammatory cytokines [16-18]. Prolonged exposure to these inflammatory mediators has been associated with reduced synaptophysin expression, synaptic loss and suppression of brain-derived neurotrophic factor (BDNF), thereby impairing neurogenesis in the hippocampus and contributing to cognitive dysfunction and memory impairment [17, 19-21].

Pro-inflammatory cytokines may also divert tryptophan metabolism toward the kynurenine pathway rather than serotonin synthesis, reducing serotonin availability and potentially contributing to low mood and anhedonia [17, 18]. In addition, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) may impair blood–brain barrier integrity, thereby amplifying neuroinflammatory processes [21, 22].

Another important mechanism implicated in depression is oxidative stress, which results from an imbalance between the production of reactive oxygen species and the antioxidant defense systems responsible for their neutralization [4, 19]. Elevated levels of reactive oxygen species may occur as a consequence of environmental exposures such as air pollution, ultraviolet radiation, and smoking. Excessive oxidative stress can damage neuronal lipids, proteins, and DNA, promoting neurodegeneration and inflammation and further enhancing inflammatory processes [4, 19].

Mitochondrial dysfunction has also been increasingly implicated in the pathophysiology of depression [1, 4, 6]. Impaired mitochondrial function leads to reduced adenosine triphosphate

(ATP) production and disturbances in cellular energy metabolism. Because the brain is one of the most energy-demanding organs in the body, deficits in energy availability may contribute to impaired cognitive performance and mood disturbances. Moreover, dysfunctional mitochondria produce increased amounts of reactive oxygen species, further exacerbating oxidative stress and neuronal damage [4, 6, 19].

Depression has additionally been associated with impaired brain glucose metabolism and insulin signaling [1, 5, 6]. Reduced neuronal glucose uptake may limit ATP production, resulting in an energy deficit that contributes to fatigue, apathy, anhedonia and cognitive impairment. Insufficient energy availability may also impair the synthesis and regulation of neurotransmitters including serotonin, dopamine, GABA, and glutamate, while disrupting neuronal network stability and membrane potential maintenance, potentially contributing to altered emotional regulation [1, 4, 6].

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis represents another important feature of depression [19, 21]. Chronic stress can result in persistent activation of the HPA axis and prolonged exposure to elevated cortisol levels, which have been associated with hippocampal atrophy, impaired neurogenesis, and disturbances in neurotransmitter systems involved in mood regulation, including serotonin and dopamine pathways [17, 19, 21].

Taken together, these mechanisms are highly interconnected and may reinforce one another, contributing to the onset and progression of depressive symptoms.

Potential Mechanisms Linking Ketogenic Diet and Depression

An increasing body of evidence suggests that the ketogenic diet may influence biological processes involved in the pathophysiology of depression and potentially contribute to the alleviation of depressive symptoms [1, 2, 5]. The following sections discuss the potential interactions between ketogenic interventions and the mechanisms underlying depression described in the previous chapter.

Modulation of Neuroinflammation

Chronic neuroinflammation is considered one of the key mechanisms involved in the pathophysiology of depression [17,18]. The anti-inflammatory effects of the ketogenic diet are thought to be mediated primarily by BHB, the principal ketone body produced in the liver during ketosis. BHB has been shown to inhibit the NLRP3 inflammasome, a multiprotein complex responsible for the maturation and release of the pro-inflammatory cytokines interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), thereby attenuating neuroinflammatory processes implicated in depression [1, 23, 24].

Elevated levels of IL-1 β have been associated with reduced synaptophysin expression and synaptic loss observed in patients with depression. Moreover, reduced concentrations of pro-inflammatory cytokines may decrease activation of indoleamine 2,3-dioxygenase (IDO), thereby limiting the diversion of tryptophan toward the kynurenine pathway and preserving serotonin synthesis, which may contribute to improvements in mood and anhedonia [17, 18, 21].

A meta-analysis of 44 controlled trials demonstrated that ketogenic interventions were associated with reductions in circulating levels of IL-6 and TNF- α [1, 5]. Increased concentrations of these cytokines have been linked to blood–brain barrier dysfunction, amplification of neuroinflammatory responses, and reductions in hippocampal volume, which are associated with cognitive impairment and memory deficits frequently observed in individuals with depression [17, 21].

Furthermore, BHB functions as a signaling molecule by activating hydroxycarboxylic acid receptor 2 (HCAR2) expressed on microglia. Activation of this receptor exerts anti-inflammatory and neuroprotective effects and may further contribute to the modulation of neuroinflammatory pathways [23].

The ketogenic diet has also been proposed to influence neurotransmission by increasing GABA availability and reducing glutamatergic excitability. Several mechanisms have been suggested, including alterations in amino acid metabolism that may favor GABA synthesis and contribute to the restoration of the excitatory–inhibitory balance within neuronal networks [1, 14].

By attenuating neuroinflammation and improving neuronal homeostasis, ketogenic interventions may contribute to improvements in mood, emotional regulation, stress resilience, and overall energy levels in individuals with depression [1, 5].

Improvement of Mitochondrial Function and Energy Metabolism

The ketogenic diet may improve mitochondrial function and cellular energy metabolism by providing an alternative energy substrate for the brain in the form of ketone bodies. Individuals with depression frequently exhibit impaired brain glucose metabolism, characterized by a reduced ability of neurons to efficiently utilize glucose for ATP production, resulting in an energy deficit [1, 5, 6, 25].

Because ketone bodies readily cross the blood–brain barrier, they can serve as an alternative and efficient energy source for the brain. Ketone metabolism has been proposed to enhance mitochondrial ATP production and improve cellular energy efficiency. Improved energy availability may contribute to the alleviation of symptoms commonly observed in depression, including chronic fatigue, apathy, and cognitive dysfunction such as impaired concentration and memory [1, 5, 23, 25].

Furthermore, the ketogenic diet has been associated with increased mitochondrial biogenesis, particularly in brain regions involved in learning, memory, and emotional regulation, including the hippocampus. Experimental evidence suggests that BHB may activate signaling pathways involved in mitochondrial biogenesis, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α), thereby promoting mitochondrial adaptation and cellular energy homeostasis [9, 12, 15].

An increased mitochondrial reserve may enhance cellular resilience to metabolic stress and contribute to the stabilization of neuronal membrane potentials and neuronal network activity. By promoting more stable energy homeostasis, ketogenic interventions may also support emotional regulation and mood stability [1, 15, 25].

In addition, ketone bodies have been shown to exert protective effects on mitochondrial function and may reduce the generation of reactive oxygen species. Consequently, ketogenic

metabolism may attenuate oxidative stress, limit neuronal damage, and potentially slow the progression of biological processes implicated in depressive disorders [1, 5, 7, 23].

Reduction of Oxidative Stress

Oxidative stress is another important mechanism implicated in the pathophysiology of depression. It is characterized by an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense systems responsible for their neutralization [4, 19].

The ketogenic diet may attenuate oxidative stress through several mechanisms. Ketone metabolism has been proposed to improve mitochondrial energy efficiency and reduce generation of reactive oxygen species. In addition, BHB may exert indirect antioxidant effects by modulating cellular signaling pathways involved in oxidative stress responses [1, 7, 23].

Furthermore, the ketogenic diet has been shown to activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a major regulator of cellular antioxidant defenses. Activation of Nrf2 promotes the expression of antioxidant enzymes, contributes to redox homeostasis and enhances glutathione metabolism. Glutathione is one of the principal endogenous antioxidants in the brain and plays a crucial role in protecting mitochondria, lipids, proteins and DNA from oxidative damage. Experimental studies have also demonstrated increased catalase activity in the hippocampus during ketogenic interventions, further supporting the antioxidant effects of ketosis [5, 8].

Mitochondrial dysfunction in depression has been associated with disturbances in mitochondrial membrane potential and increased production of reactive oxygen species. Ketogenic metabolism has been proposed to increase the expression of mitochondrial uncoupling proteins, which may lower mitochondrial membrane potential and thereby reduce reactive oxygen species generation. Because oxidative stress and mitochondrial dysfunction reinforce one another, the antioxidant properties of ketogenic metabolism may simultaneously improve cellular energy production and limit neuronal injury [4, 5, 8].

Excessive oxidative stress contributes to neuronal damage and has been associated with hippocampal dysfunction, impaired synaptic plasticity and reduced expression of BDNF, a key mediator of neurogenesis and neuronal survival. These alterations may contribute to cognitive impairment and depressive symptoms [17, 19, 20].

Taken together, the available evidence suggests that ketogenic interventions may attenuate oxidative stress and restore redox balance, thereby reducing neuroinflammation and potentially alleviating symptoms commonly observed in depression, including chronic fatigue, apathy, and anhedonia [1, 2, 5, 25].

Modulation of Neurotransmitter Systems

Dysregulation of neurotransmitter systems represents one of the central neurobiological features of depression. The disorder has been associated with disturbances in the balance between excitatory and inhibitory neurotransmission, including alterations in glutamatergic and GABAergic signaling [1, 2, 5].

The ketogenic diet may contribute to the restoration of this balance through several mechanisms. During ketone metabolism, increased production of acetyl-coenzyme A (acetyl-CoA) may modify tricarboxylic acid cycle flux and influence amino acid metabolism in a manner that favors GABA synthesis while reducing glutamatergic excitability. Consequently, ketogenic metabolism has been proposed to increase GABA availability and promote a more stable excitatory–inhibitory balance within neuronal networks [8, 14, 23].

During ketosis, astrocytes may also increase acetate uptake, which can subsequently be utilized for glutamine synthesis. Because glutamine serves as an important precursor for GABA production, these metabolic adaptations may further contribute to enhanced GABAergic neurotransmission. Increased GABA availability may help reduce anxiety, emotional instability and stress sensitivity frequently observed in individuals with depression [2, 8, 14].

By reducing the production of pro-inflammatory cytokines such as IL-6 and TNF- α , the ketogenic diet may decrease activation of indoleamine 2,3-dioxygenase (IDO), thereby limiting the diversion of tryptophan toward the kynurenine pathway and preserving serotonin synthesis.

Increased serotonin availability may contribute to improvements in mood, reduced anhedonia and better sleep quality [17, 18].

Furthermore, the ketogenic diet has been associated with increased adenosine signaling. Adenosine exerts inhibitory effects within the central nervous system, contributes to the stabilization of neuronal networks and reduces neuronal hyperexcitability while promoting more efficient energy utilization. These effects may potentially contribute to improvements in fatigue and cognitive function [8, 11, 13].

Research also suggests that ketogenic interventions may influence noradrenergic neurotransmission in brain regions involved in mood regulation, including the hippocampus. Modulation of norepinephrine signaling may potentially contribute to improvements in motivation, energy levels and emotional responsiveness [8].

Taken together, these findings suggest that the ketogenic diet may attenuate excessive excitatory neurotransmission while simultaneously strengthening inhibitory and mood-stabilizing pathways. Moreover, by reducing inflammation-related tryptophan degradation, ketogenic interventions may help preserve serotonin availability and support emotional and cognitive functioning in individuals with depression [1, 2, 17].

Effects on Brain Glucose Metabolism and Insulin Signaling

Impaired brain glucose metabolism has increasingly been recognized as a feature of depressive disorders. Brain glucose hypometabolism is characterized by reduced efficiency of glucose uptake and utilization by neurons and other brain cells, resulting in diminished ATP production and reduced energy availability. Clinically, this energy deficit may contribute to symptoms commonly observed in depression, including chronic fatigue, apathy, lack of motivation and cognitive difficulties such as impaired concentration and memory [1, 6, 25].

The ketogenic diet provides an alternative energy substrate for the brain in the form of ketone bodies. Because ketone bodies readily cross the blood–brain barrier and can be directly utilized by mitochondria, they may bypass some of the limitations associated with impaired glucose metabolism and support ATP production despite reduced glucose utilization [8, 23].

Some evidence also suggests that depression may be associated with brain insulin resistance, a condition characterized by impaired responsiveness of neural cells to insulin signaling. Altered insulin signaling may contribute to disturbances in neuronal metabolism, reduced mitochondrial efficiency and impaired energy homeostasis [2, 5, 25].

Due to its substantial restriction of carbohydrate intake, the ketogenic diet lowers circulating glucose and insulin concentrations. Ketogenic interventions have been associated with improvements in systemic insulin sensitivity and may also favorably influence brain insulin signaling. These metabolic adaptations may help restore metabolic homeostasis and promote greater stability of neuronal network activity, potentially contributing to improved mood regulation [1, 5].

Furthermore, ketone utilization may reduce glycolytic demand while potentially preserving glucose for other metabolic pathways, including antioxidant defense mechanisms. Because brain energy metabolism influences immune function, neurotransmission, and neuronal plasticity, improvements in metabolic homeostasis may have widespread effects on multiple biological systems implicated in depression [2, 5, 6].

Taken together, the available evidence suggests that by providing an alternative energy substrate and potentially improving insulin signaling, ketogenic interventions may contribute to the alleviation of depressive symptoms and the restoration of brain metabolic function [1, 2, 5].

Alterations in the Gut–Brain Axis and Microbiota

Growing evidence suggests that gut dysbiosis may contribute to chronic low-grade inflammation and has been implicated in the pathophysiology of depression. Alterations in the composition and function of the gut microbiota may influence immune responses, neurotransmitter production and metabolic pathways involved in mood regulation [22, 26].

According to current evidence, the ketogenic diet may influence the gut–brain axis primarily through alterations in microbial composition and metabolic activity. Ketogenic interventions have been associated with an increased abundance of *Akkermansia muciniphila*, a bacterial

species that has been linked to improved intestinal barrier integrity and reduced intestinal inflammatory signaling. By strengthening gut barrier function and attenuating inflammatory responses, these changes may contribute to lower levels of pro-inflammatory mediators and reduced systemic inflammation, processes that have been implicated in depression [26, 27].

Preliminary evidence also suggests that alterations in gut microbiota composition may influence GABAergic neurotransmission through microbiota-derived metabolites and gut–brain communication pathways. Enhanced GABA signaling may potentially contribute to improved emotional regulation, reduced anxiety and greater mood stability [13, 26].

Some studies have additionally reported an increased abundance of *Bacteroides* species during ketogenic interventions. These bacteria may influence glutamate metabolism and excitatory neurotransmission, potentially contributing to the restoration of the excitatory–inhibitory balance that is frequently disrupted in depressive disorders [2, 27].

Furthermore, by promoting a more favorable intestinal environment, ketogenic interventions may reduce inflammatory activity and support metabolic homeostasis. Because the gut microbiota influences immune function, energy metabolism and neurotransmitter signaling, modulation of the gut–brain axis may represent another pathway through which ketogenic interventions could potentially alleviate depressive symptoms [2, 26].

Taken together, the available evidence suggests that the effects of ketogenic interventions on inflammation, mitochondrial function, oxidative stress, neurotransmission and the gut–brain axis are highly interconnected and may collectively contribute to improvements in mood and cognitive functioning in individuals with depression.

Current Clinical Evidence on the Ketogenic Diet in Depression

Despite growing interest in metabolic psychiatry, the number of studies investigating the relationship between the ketogenic diet and improvement of depressive symptoms remains limited. Most of the available evidence comes from small pilot studies and case reports, while large, long-term randomized controlled trials are still lacking [1, 2, 5].

Evidence from Case Reports and Pilot Studies

Gao et al. reported greater reductions in depressive symptoms among participants following a ketogenic diet compared with those receiving the control dietary intervention. Outcomes were assessed using the 9-item Patient Health Questionnaire (PHQ-9). However, the observed between-group effect was modest and the clinical significance of these findings remains uncertain. In addition, the relatively short duration of follow-up precluded assessment of the long-term efficacy and sustainability of the intervention [3].

Brietzke et al. demonstrated significant reductions in symptoms of depression, anxiety, and anhedonia among patients following a medically supervised ketogenic diet. Improvements were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS), the Generalized Anxiety Disorder-7 (GAD-7), and the Snaith–Hamilton Pleasure Scale (SHAPS). However, this open-label pilot study included only a small number of participants and lacked a control group, limiting the generalizability of the findings [28].

Similarly, Calabrese et al. reported reductions in symptoms of depression and anxiety in all participants undergoing ketogenic metabolic therapy, as measured by the PHQ-9 and GAD-7 scales. Participants also experienced weight loss and improvements in metabolic health markers. Nevertheless, the study was conducted in a very small sample without a control group, making it impossible to exclude placebo effects and other nonspecific treatment factors [25].

In contrast, Mela et al. found that a Mediterranean diet resulted in greater improvements in depressive symptoms than a ketogenic diet, although the ketogenic intervention was associated with reduced impulsivity. Outcomes were assessed using the Beck Depression Inventory (BDI) and the UPPS Impulsive Behavior Scale. Importantly, participants in this study were individuals with obesity rather than patients diagnosed with MDD. Furthermore, the study involved a small sample size and a short follow-up period, limiting conclusions regarding long-term effects [29].

Finally, Hongler et al. initiated the KETO-MOOD trial to investigate the effects of a ketogenic diet on depressive symptoms in patients with MDD. However, this randomized controlled trial is still ongoing, and clinical outcome data are not yet available [26].

The main characteristics and findings of the available clinical studies are summarized in Table 1.

Table 1. Summary of clinical studies investigating the ketogenic diet in depression

Study	Study design	Population	Intervention	Main findings
Gao et al. (2025) [3] <i>Ketogenic Diet for Treatment-Resistant Depression: A Randomized Clinical Trial</i>	RCT	88 adults with treatment-resistant depression	KD compared with control diet for 6 weeks	Greater reduction in depressive symptoms was observed in KD group after 6 weeks
Brietzke et al. [28] <i>Medically supervised ketogenic diet as an adjunctive treatment for moderate to severe depression: A pilot study</i>	Pilot study	Adults with moderate to severe depression	Medically supervised ketogenic diet as an adjunctive treatment	Improvements in depressive symptoms, anxiety and anhedonia
Calabrese et al. (2024) [25] <i>Complete remission of depression and anxiety using a ketogenic diet: case series</i>	Case series	3 adults with depression and anxiety disorders	Personalized whole food animal-based ketogenic metabolic therapy for 12-16 weeks	All participants achieved remission of depression and anxiety symptoms. Weight reduction and improvement in metabolic health was observed.
Mela et al. [29] <i>Ketogenic diet is less effective in ameliorating depression and anxiety in obesity than Mediterranean diet: A</i>	Pilot study	Adults with obesity and depressive/anxiety symptoms	KD versus Mediterranean diet	Both interventions improved in mood symptoms, but Mediterranean diet showed greater improvements in

<i>pilot study for exploring the GUT-brain axis</i>				depression and anxiety
Hongler et al. [26] <i>KETO-MOOD: Ketogenic Diet for Microbiome Optimazation and Overcoming Depression - A Protocol for a Randomized Controlled Trial</i>	Protocol for a RCT	Adults with a depression	Planned ketogenic intervention compared to healthy, insulin-lowering, non-ketogenic diet	This study aims to evaluate the efficacy of the KD in alleviating MDD symptoms

Abbreviations: RCT, randomized controlled trial; KD, ketogenic diet; MDD, major depressive disorder.

Risks, Limitations and Future Directions

Overall, the existing evidence suggests that the ketogenic diet may have the potential to reduce depressive symptoms [2, 3, 5]. However, these findings should be interpreted with caution due to several methodological limitations. Most available studies are characterized by small sample sizes, short intervention periods and lack of randomized controlled designs or adequate control conditions, which limits the generalizability of results [3, 10].

In addition, long-term adherence to a ketogenic diet may be challenging and may be associated with adverse effects such as constipation, nausea, fatigue, headache, and potential nutritional deficiencies [1, 2, 5].

Furthermore, the long-term safety and clinical effectiveness of ketogenic interventions for depression have not yet been established. The current evidence is based predominantly on short-term studies, limiting conclusions regarding the durability of treatment effects and long-term metabolic outcomes [2, 6].

Therefore, future research should focus on large-scale, randomized controlled trials with longer follow-up periods and standardized ketogenic protocols. Particular attention should also be given to identifying patient subgroups most likely to benefit from ketogenic interventions, as well as potential biological or metabolic predictors of treatment response [2, 5].

Conclusions

Depression is one of the most prevalent psychiatric disorders worldwide and a substantial proportion of patients do not achieve full remission with conventional treatment approaches [3, 5]. Increasing evidence suggests that the pathophysiology of depression involves not only disturbances in neurotransmitter systems but also neuroinflammation, oxidative stress, mitochondrial dysfunction, impaired energy metabolism and alterations in the gut–brain axis [1, 2, 6]. Consequently, metabolic psychiatry has emerged as a promising framework for understanding the relationship between systemic metabolism and brain function [5].

Current evidence suggests that the ketogenic diet may influence several of these biological pathways simultaneously, including providing an alternative energy source for the brain, improving mitochondrial function, reducing neuroinflammation and oxidative stress, and modulating neurotransmitter systems involved in mood regulation [1, 5, 8].

Although the available clinical findings are encouraging, the current evidence base remains limited. Most studies have involved small sample sizes, short follow-up periods, and methodological limitations. Therefore, larger randomized controlled trials with longer durations are required to determine the efficacy, safety, and long-term effects of ketogenic interventions in patients with depression. At present, the ketogenic interventions cannot yet be considered an evidence-based treatment for depression, but they may represent a promising adjunctive strategy in selected patients [2, 3].

Future research should aim to clarify mechanisms of action, establish standardized dietary protocols, and determine long-term safety and efficacy in clinical populations with depressive disorders [5, 6].

Disclosure

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