Ketone bodies and inflammation modulation: A mini-review on ketogenic diet’s potential mechanisms in mood disorders

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Abstract: Mental disorders such as depression and anxiety inflict significant burdens on individuals and society. Commonly prescribed treatments often involve cognitive therapy and medications. However, for patients resistant to these conventional methods, alternative therapies like the Ketogenic Diet (KD) offer a promising avenue. KD and its key metabolite, β-hydroxybutyrate (BHB), have been hypothesized to alleviate mental disorders through anti-inflammatory actions, a crucial pathway in the pathophysiology of depression. This mini-review examines 15 clinical trials exploring the influence of KD and BHB on inflammation and their potential roles in managing mental disorders. Both human and animal studies were scrutinized to elucidate possible cellular and molecular mechanisms. Out of the 15 trials, 10 reported reduced levels of at least one inflammatory mediator or mRNA post KD or BHB treatment, while two observed an elevation in anti-inflammatory agents. These findings suggest that KD and BHB could modulate cellular inflammatory pathways, highlighting their potential for therapeutic application in mental disorders.

Introduction

Common mental disorders (CMD) refer to two main diagnostic categories: depressive and anxiety disorders. According to the World Health Organization, in 2015, the proportion of the global population with depression was estimated to be 4.4%. The prevalence was more common among females (5.1%) than males (3.6%) (World Health Organization, 2017). The proportion of anxiety disorders was estimated to be 3.6%, which also appears to be more common among females (4.6%) than males (2.6%) (World Health Organization, 2017).
Both these mental disorders are a leading cause of disability, imposing a substantial burden on individuals and society (Friedrich, 2017; Stein and Craske, 2017).

While cognitive therapy and medications are the first-line treatment for CMD, 10%–30% of the patients do not respond to antidepressant medicines. Additionally, they exhibit symptoms such as declined physical health and social/occupational function, or even suicidal intentions (Pilkington, 2018). Therefore, alternative and complementary therapies for the prevention and treatment of CMD are urgently needed.

Though the pathology of CMD is not fully understood, the mutual and functional role of the immune system in the development of CMD symptomology has been highlighted by recent findings. Inflammation, mainly mediated by cytokines and chemokines that are secreted by immune cells, is generally considered a defense mechanism upon infection. However, chronic and excessive inflammation may interfere with synaptic remodeling, transcription, and epigenetics. It may also harm the integrity of neuronal function, influence neurocircuitry and/or neurotransmitter systems, and produce behavioral alternations (van Velzen et al., 2017). Mounting evidence indicates that inflammatory cytokines are responsible for the development of CMD. For instance, epidemiological studies using data collected from 147,478 individuals from the UK Biobank and 2,905 from the Netherlands Study of Depression and Anxiety indicate that the inflammation level was associated with core depressive and anxiety symptoms of low mood, anhedonia, and other symptoms (van Eeden, 2022; Milaneschi et al., 2021). In animal model studies, evidence shows that activated immune responses are observed in many CMD animal models, and treatment with several kinds of cytokines could produce depressive and anxiety-like behaviors (Camara et al., 2013; Murray et al., 2013). Furthermore, CMD occurs more frequently in those who already have medical disorders associated with immune dysfunction (Galecki and Talarowska, 2018). Therefore, anti-inflammatory agents and treatments are considered effective ways to fight CMD.

The ketogenic diet (KD) is a dietary regimen that contains high fat and low carbohydrate content. It is an established treatment for refractory epilepsy, and a potential strategy for treating a number of non-epileptic neurological disorders. Moreover, KD is being actively investigated as a treatment for various non-neurological conditions, including mood disorders (Malley et al., 2020; Hashim and Malley, 2017). There is growing interest in using KD as a treatment option for CMD, as it may reduce inflammation and improve mood and cognitive function. KD is a high-fat, low-carbohydrate diet that forces the body to burn fat for energy instead of carbohydrates. This results in ketone production, which can have anti-inflammatory properties.

KD is typically started with a low-carbohydrate diet and then gradually increased to a high-fat, low-carbohydrate diet. KD can be initiated with a low-carbohydrate diet and then gradually increased to a high-fat diet to allow the body to adapt. This adaptation period is known as the "ketosis phase." After this phase, the diet is continued indefinitely.

Ketone supplements, such as β-hydroxybutyrate (BHB), are also being investigated as a potential treatment for CMD. BHB is a ketone body produced in the liver during ketosis and is used as an energy source by the brain. BHB supplements are available as a powder or liquid and can be taken orally or injected. Studies have shown that BHB can have anti-inflammatory properties and may improve cognitive function and mood in people with CMD.

Inclusion and exclusion criteria
For search (2), randomized crossover or parallel controlled trials assessing the impact of KD or BHB on human inflammation status measures were included in the current analysis. There were no exclusion criteria for study duration, age, sample size, or health status. Studies assessing the impact in animal models were separated from human trials and analyzed separately. Studies of case reports were excluded.

Data extraction
Data were extracted from 15 studies that were selected to meet the inclusion and exclusion criteria. Intervention type and duration, sample characterization, subject status, study duration, sample size, and health status were recorded.
design, assay, and inflammatory mediators were extracted from each study to provide descriptive characteristics of participants. For animal studies, the findings have been discussed in a non-systematic way as an elaboration on the proposed mechanisms.

Results

For the results of search (2), based on the PRISMA principles shown in Fig. 1, we retrieved 15 articles that have been summarized in Table 1.

Among the studies, 13 studies included KD as an intervention (Bock et al., 2018; Bosco et al., 2018; Castaldo et al., 2021; Rhyu and Cho, 2014; Cipryan et al., 2020a, 2020b; Paoli et al., 2021; Bertoli et al., 2015; Kong et al., 2020; Khodabakhshi et al., 2021; Rosenbaum et al., 2019; Monda et al., 2020; Shaw et al., 2020), while only 2 studies employed ketone body administration as an intervention (Shaw et al., 2020; Martin-Arrowsmith et al., 2020). Alteration of multiple cytokines or other inflammatory mediators such as adiponectin, resistin, etc., were reported.

Among the studies, 10 of 15 (66.7%), reported at least one inflammatory mediator (C-reactive protein (CRP), leptin, interleukin (IL)-1β, IL-2, IL-6, IL-12p40, interferon (IFN)-γ and/or tumor necrosis factor (TNF)-α (Bosco et al., 2018; Castaldo et al., 2021; Cipryan et al., 2020b, 2020a; Kong et al., 2020; Shaw et al., 2020; Khodabakhshi et al., 2021, Monda et al., 2020) or the mRNA of the indicated inflammatory mediators (IFN-γ mRNA, Shaw et al., 2020) was decreased by KD or BHB intervention. However, 3 studies reported that no changes were observed (Bock et al., 2018; Rhyu and Cho, 2014). Further, 2 reported that an anti-inflammation mediator (adiponectin and/or IL-10) was increased (Rosenbaum et al., 2019; Monda et al., 2020; Bertoli et al., 2015). The selected studies conducted on humans showed that KD has great potential in treating inflammatory diseases, showing the potential to be utilized as a treatment for CMD based on the inflammation hypothesis of the pathology of CMD. However, the evidence of BHB is far from convincing, and further studies are warranted. The details of the above studies are listed as Table 1.

Discussion

Inflammation is our body’s defense system protecting us against infection, cellular damage, and other harmful agents, both exogenously and endogenously (Suzuki, 2018a; Suzuki et al., 2020). During inflammation, cytokines play a significant role in mediating cellular signaling and immunological responses. Cytokines are a category of small proteins (5~20 kDa) secreted by a broad range of cells, including immune cells such as macrophages, lymphocytes, mast cells, endothelial cells, fibroblasts, myocytes, adipocytes, and other kinds of cells (Ma et al., 2020; Suzuki, 2018b). The subcategories of cytokines include chemokines,
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<td>Khodabakhshi et al. (2021)</td>
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<td>Rosenbaum et al. (2019)</td>
<td>Ketogenic diet 4 weeks</td>
<td>KD, n = 17 Adults</td>
<td>Overweight/obese patients</td>
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<td>Adiponectin, CRP↑, pre- and post-intervention IL-6→</td>
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<tr>
<td>Martin-Arrowsmith et al. (2020)</td>
<td>Ketone body ketone monoester, twice-time a day administration 360 mg/kg bw Exercise involved, only pre-exercise results are pooled</td>
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Table 1 (continued)

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<th>Study</th>
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<td>IL-10↑, pre- and post-KD intervention IL-6→</td>
</tr>
</tbody>
</table>

Notes: KD, ketogenic diet; KB, ketone bodies. RCT; randomized, controlled trial; ALOX, arachidonate 5-Lipoxygenase; COX, cyclooxygenase; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; PCR: polymerase chain reaction; TNF, tumor necrosis factor; IFN, interferon; CRP, C-reactive protein; MCP, monocyte chemotactic protein; and bw, body weight. * Pre means the time point immediately before a KD or BHB intervention, while Post means the time point immediately after a KD or BHB intervention. **Moderately trained indicates at least three exercise sessions/week.

interferons, interleukins, lymphokines, and tumor necrosis factors, all involved in fighting off infections and other immune responses (Aw et al., 2018). However, inflammation that acts against wrong stimuli may induce unwanted cytokine production, thus bringing undesired consequences. A large body of studies has reported that pro-inflammatory or inflammatory cytokines increase in CMD patients (Hou et al., 2017; Gelman, 2019; Zou et al., 2018; Martinez et al., 2018; Jia et al., 2019; Petralia et al., 2019). The evidence on the cytokine secretion profile collected from papers published in the recent five years is depicted in Fig. 2.

According to a case-controlled study conducted in generalized anxiety disorder (GAD) patients, significantly higher ratios of TNF-α/IL-10, TNF-α/IL-4, IFN-γ/IL-10, and IFN-γ/IL-4 were found in the GAD group compared to the control group (patient group: n = 54; control group: n = 64) (Hou et al., 2017). In pregnant women with severe anxiety and depression, the levels of Th1-(IL-6, TNF-α, IL-2, IFN-γ), Th17-(IL-17A), and Th2-(IL-9, IL-10, and IL-13) were higher than those in the control group (n = 139, patient group; n = 40, control group) (Gelman, 2019). In one report, patients with major depressive disorders had significantly higher levels of IL-1β, IL-10, and TNF-α but significantly lower levels of IL-8 (n = 117, patient group; n = 102, control group) (Zou et al., 2018). In another report, IL-1, IL-6, TNF-α, IFN-γ, and IL-10 were found to be associated with depression scores in people with alcohol and drug use disorder (n = 80, patient) (Martinez et al., 2018). Further, a significantly positive correlation between serum cortisol levels and Hamilton Depression Rating Scale scores was observed in 89 male depression patients (Jia et al., 2019). In women with postpartum depression, significant fluctuation of TNF-α and IL-18 were found (Petralia et al., 2019). Therefore, targeting pro-inflammatory and inflammatory cytokines and their signaling pathways might be novel strategies to treat CMD.

Although the mechanism of inflammation in CMD has not been fully explained, the loss of regulation of inflammatory agents and neurotransmitters seems to be the key. The imbalance of neurotransmitters, including serotonin (5-HT), norepinephrine, and dopamine has been reported and treated to be the reason for CMD (Yan, 2018; Naoi et al., 2018). Meanwhile, inflammatory cytokines trigger neuroinflammation, microglial activation, and disturbance of neurotransmitters, resulting in CMD pathophysiological process (Morris et al., 2016). Let us consider the loss of the regulation process of 5-HT as an example. According to the cytokine theory, the initiation of stress increases the production of cytokines, including TNFs, and ILs. IFNs may contribute to the pathophysiological process of CMD. Increased levels of the abovementioned inflammatory cytokines may activate the production of the indoleamine 2,3 dioxygenase (IDO), with subsequent production of tryptophan (TRP) catabolites along the IDO pathway, decreasing the availability of TRP and serotonin and contributing to the progress of CMD (Morris et al., 2016). Conversely, phytochemical supplementation that suppresses pro-inflammatory cytokines, thus inhibiting type A monoamine oxidase (MAOA), has been reported to be efficient in relieving depression (Yan, 2018). Therefore, the use of anti-inflammatory compounds and diets that exhibit anti-inflammatory properties may be a strategy for CMD treatment.

Introduced as a treatment for refractory epilepsy in the first place, the KD has been reported for its anti-inflammatory properties in recent years. This provides a potential contributing role in treating CMDs, based on the inflammation hypothesis of the pathology of CMD. For example, in a lipopolysaccharide (LPS)-induced inflammation model in rats, a 2-week administration of KD attenuated LPS-induced fever, and reduced blood and hippocampal IL-1β concentration to alleviate inflammation (Baura et al., 2018). In another rodent inflammation model built by inducing a hind paw inflammation, a KD significantly reduced decreased paw swelling, plasma extravasation, and the peripheral inflammatory response (Ruskin et al., 2021). In a paper published in 2016, after a one-month feeding period of KD mice then received LPS by intraperitoneal injection it was reported that KD mice had significantly lower expression of nuclear factor-kappa B (NF-κB), IL-6, and TNF-α (Nandivada et al., 2016). These
studies showed that a KD has excellent potential in serving as an anti-inflammation therapy for inflammation. In the neuroscience field, KD also attracts great attention. In a memory impairment and central nervous system-inflammation murine model, pre-feeding of a one-week KD (12.2 g polyunsaturated fatty acids in 100 g per KD) decreased circulating inflammatory cytokines including IL-1β, IL-6, TNF-α, IL-17A, IFN-γ, MCP-1, MIP-1α and MIP-1β (Kim et al., 2012). In a spinal cord injury rat model, KD suppressed the NF-κB pathway and the expression of TNF-α, IL-1β, and IFN-γ (Lu et al., 2018). In another mouse model, motor dysfunction was induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment, and pre-treatment of KD decreased IL-1β, IL-6, TNF-α (Yang and Cheng, 2010).

The anti-inflammatory properties of a KD may be attributed to the ability to activate peroxisome proliferator-activated receptor-gamma (Jeong et al., 2011; Zhang et al., 2018), subsequently decreasing systemic inflammation (Zhang et al., 2018). Furthermore, increasing evidence shows that the enhanced levels of BHB, the metabolite of fatty acids during a KD, may contribute to playing an anti-inflammatory role (Prattichizzo et al., 2018; Zitvogel et al., 2017).

Although clinical trials on patients with common mental disorders aiming to elicit the anti-inflammatory properties of BHB have not yet been carried out, animal studies have provided some clues. For example, exogenous ketone body administration has been shown to decrease anxiety-related behaviors evaluated by an open-arm system in rodents (83-days sub-chronic beta-hydroxybutyrate-mineral salt supplementation) (Kovács et al., 2018), possibly by interacting with the Adenosine A1 receptor (Kovács et al., 2018). In another study, BHB administration has also been shown to reduce depressive-like behaviors in rodents as evaluated by chronic unpredictable stress and sucrose preference experimental methods (Kovács et al., 2018). In situ BHB administration has been reported to suppress macrophage/microglia activation (Huang et al., 2018). Although the underlying mechanisms have not been elucidated yet, one of the possible mechanisms to ameliorate depressive and anxiety symptoms is by suppressing inflammation (Kong et al., 2017).

The anti-inflammatory properties of BHB have been reported extensively. A study conducted in a rodent model revealed the protective effect of BHB on neuroinflammation. In this study, repeated BHB administration reduced depressive and anxiety behaviors in animals undergoing chronic unpredictable stress (Kong et al., 2017). Additionally, pre-treatment of BHB reduced hippocampal IL-1β and TNF-α (Yamanashi et al., 2017). BHB could alleviate inflammation by attenuating NLR family pyrin domain containing (NLRP)-3 inflammasome formation in IL-1β/IL-18 over-expression mice (Yamanashi et al., 2017). Suppression of the activation of the NLRP3 inflammasome by preventing K+ efflux and reducing apoptosis-associated speck-like protein with a caspase-recruitment domain (ASC) oligomerization and speck formation in human monocytes has also been documented (Kajitani et al., 2020). In BV2 cells, BHB supplementation inhibited LPS-induced inflammatory responses and NLRP3 inflammasome protein level, shifting the activation of macrophages/microglia from the proinflammatory M1 to the anti-inflammatory M2a type (Deng et al., 2021). On the other hand, when the ketolytic, rate-limiting enzyme SCOT (succinyl-CoA:3-ketoacid-CoA transferase 1; encoded by Oxc1) was deleted, markers of sterile inflammation and macrophage infiltration were shown to be attenuated in mice that underwent transverse aortic constriction surgery. Further, the NLRP3 expression was
also reduced, indicating that elevated circulating BHB might be linked to reduced inflammation through an NLRP3-mediating manner (Goldberg et al., 2017).

Calorie restriction is well known for its anti-inflammatory activities (Ottaviano and Zaman, 2023). Other studies also reported that BHB might exert its anti-inflammatory effects as a calorie restriction mimic (Kim et al., 2019). In one report, BHB administration upregulated Forkhead Box1 (FoxO1) and its target genes catalase/manganese superoxide dismutase (MnSOD). Both play critical roles in quenching inflammation-induced reactive oxygen species, thus ameliorating renal inflammation in aging rats (Kim et al., 2019) by down-regulating TNFSF6, TNF-α, PI3K, NF-κB and toll-like receptor 1 on LPS-stimulated macrophages (Qiao et al., 2020). Another role of BHB during anti-inflammation might be as the inhibitor of histone deacetylase (HDAC), as HDAC inhibition is well-known to have anti-inflammatory effects. For example, in HEK293 cells, HDAC activity decreased with the elevation of BHB concentration, indicating that BHB function as an HDAC inhibitor is dose-dependent (Shimazu et al., 2013).

In the same study, it was also shown that dietary BHB exhibited protective effects on cells against oxidative stress via up-regulation of FoxO3a, which shares a similar function as FoxO1, and its target gene, catalase and mitochondrial MnSOD2 (Shimazu et al., 2013). To summarize, numerous studies also show the potential role of BHB in the treatment of CMD. However, since most of the studies are conducted in animals, and the mechanisms are speculative, further studies are urgently encouraged to validate the safety, effectiveness, and mechanisms of BHB application for human CMD treatment.

Conclusions

The anti-inflammatory properties of KD or BHB, the biomarker metabolite during KD administration, are attracting the attention of researchers. In this review, we summarized 15 clinical trials that employed KD or BHB to study their effects on the prevention and treatment of inflammation. Most of them documented favorable results. A KD or BHB-based therapy may thus contribute to relieving neuroinflammation and depressive and anxiety behaviors and have the potential to become a part of the CMD-treatment strategy.

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Ethics Approval: Not applicable.

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References


**Supplementary Materials**

**TABLE S1.** Prisma checklist