The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disorders

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The neuroimmune system plays a crucial role in the regulation of mood disorders. Moreover, recent studies show that brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is a key regulator in the neuroimmune axis. However, the potential mechanism of BDNF action in the neuroimmune axis’ regulation of mood disorders remains unclear. Therefore, in this review, we focus on the recent progress of BDNF in influencing mood disorders, by participating in alterations of the neuroimmune axis. This may provide evidence for future studies in this field.

Keywords: BDNF, neuroimmune axis, mood disorders, depression, inflammation, cytokines

INTRODUCTION

Mood disorders are one of the most common mental disorders in the world, especially in western society. Epidemiological studies have found that there are approximately 350 million people affected by depression in the world, and the number is increasing year on year (1, 2). According to the results of the global burden of disease study, years lost to disability of depression ranks first among the top 10 disabling diseases in the world (3). The main clinical features are marked by consistent emotional upsurge or depression, often accompanied by corresponding changes in thinking and behavior (4). The performance of mood disorders is highly variable. Lighter ones may respond to certain negative life events, while heavier ones may become a seriously recurrent or even chronic disabling disorder. Clinically, mood disorders can be divided into four types: depressive episode, manic episode, bipolar disorder, and a persistent mood disorder. It not only brings severe mental pain to patients but also leads to other diseases, such as heart disease and cerebrovascular diseases. However, the pathogenesis of mood disorders is still unclear, so it is difficult for patients to be cured. Although mood disorders can currently be treated with drugs, psychotherapy or a combination thereof, the efficacy is limited and side effects may also occur (5, 6). It is therefore necessary to explore the etiology and mechanism of mood disorders to treat and prevent mood disorders.

There are many theories about the nosogenesis of depression disorder, such as monoamine neurotransmitter hypothesis, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, neurotrophic hypothesis and cytokine hypothesis (7, 8). In recent years, more and more studies have focused on the relationship between mood disorders and neuroimmune regulation (9). Many neurotrophins are associated with the pathogenesis of mood disorders, such as the nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (10, 11). Several studies have shown that BDNF may be indispensable to the neuroimmune regulation of mood disorders. However, the potential mechanism for BDNF to affect mood disorders, by participating in changes in the neural-immune axis, has not been elucidated. In this review, we summarize...
the latest progress in the role of BDNF in the neuroimmune axis regulation of mood disorders. It may provide new ideas for the research and treatment of mood disorders in the future.

**BDNF AND MOOD DISORDERS**

BDNF, an important member of the neurotrophic factor family, is a protein synthesized in the brain and widely distributed in the central nervous system (CNS), as well as the peripheral nervous system (12). It can promote the survival, growth, differentiation, and development of neurons and plays a crucial role in the neural structure and functional plasticity (13, 14). A large number of human and animal studies have implicated the close links between BDNF and the occurrence and treatment of various diseases, including schizophrenia (15), Alzheimer’s disease (16, 17), mood disorders (18), and Parkinson’s disease (19).

**Studies About BDNF in Depression**

The neurotrophic hypothesis suggests that pathological changes in brain areas associated with depression, are closely related to BDNF expression and functional down-regulation (20). Animal models of depression suggest the vital function of BDNF in the pathophysiological mechanism of depression. In animal experiments, chronic stress and depression conditions decreased BDNF expression, increased apoptosis and decreased regeneration of neurons in the hippocampus, and also decreased BDNF expression in other parts of the brain (21, 22). However, whether these speculations apply to humans still remain to be tested in clinical studies. A large number of clinical studies have found that various kinds of stress can reduce the activity of the BDNF pathway in the hippocampus and prefrontal cortex (23–25). The postmortem studies of Karege et al. (26) reported that the analysis of brain tissue samples from patients with depression after self-killing found that BDNF and TrkB expression in the hippocampus decreased. Moreover, in the hippocampus of patients who have received antidepressant treatment before their death, BDNF and TrkB expression increased (26). The vast majority of studies have found abnormally lower serum BDNF levels in patients with depression than that of people without depression (25, 27, 28). Ristevski-Dimitrovskva et al. found that the serum BDNF level of depressed patients was lower than that of the control group (29), while significantly higher BDNF levels were found after antidepressant treatment (24). A meta-analysis showed that the serum or plasma BDNF increased during treatment in severe mental illness inpatients, but was not restored (18). Treatment with an antidepressant, Agomelatine, could increase the hippocampal BDNF level and BDNF positive neurons in CUMS rats (30). Kreinin et al. found that the serum BDNF level was positively correlated with depression in women with severe MDD, which further supported the role of BDNF in the pathogenesis and treatment of MDD (31). Moreover, increased BDNF levels suggest that BDNF may serve as a marker for a therapeutic response to ECT in MDD patients (32). Thus, it has been speculated that BDNF may be a biomarker of depression. But to understand the role of BDNF in depression, it is also necessary to further clarify the regulatory factors affecting BDNF expression, namely the upstream and downstream signaling pathways of BDNF in the nervous system.

**BDNF and Neurotransmitters in Depression**

The monoaminergic hypothesis is also one of the most important hypotheses to study in the pathogenesis of depression. It points out that depression may be caused by low levels of monoamine neurotransmitters in the brain (33). Meanwhile, the function of BDNF is closely related to the plasticity of 5-HT, choline lipids, DA neurons and the survival of central neurons. For example, BDNF could promote the regeneration of 5-HT neurons in the CNS, so the large consumption of 5-HT in the CNS reduces the BDNF level, which leads to the atrophy and death of nerve cells, affects neural plasticity, and thus aggravates depressive symptoms (34). In addition, the regulatory effect of BDNF on the 5-HT2A receptor level is also an important mechanism of BDNF’s role in affective disorder (35). A study suggested that BDNF was implicated in the neuroprotective effects of the selective 5-HT1A receptor agonist, 8-OH-DPAT, against CA1 neurons apoptotic death after transient global cerebral ischemia (36). BDNF also plays an essential role in the mesolimbic DA pathway. Studies have shown that the blockade of BDNF activity in the ventral tegmental area-nucleus accumbens pathway exerts an antidepressant-like activity in rodent models of stress (37–39). BDNF controls the expression of the D3 receptor in part of the brain, and induction of BDNF by antidepressant treatments is associated with its behavioral activity (40).

**Signaling Pathway of BDNF in Depression**

Tyrosine receptor kinase B (TrkB), a member of the tyrosine kinase family, can specifically bind to BDNF with a high affinity (41). Comprehensive research has indicated that BDNF is involved in the regulation of CNS, mainly by binding to TrkB (Figure 1). BDNF activates intracellular tyrosine kinase activity by binding to TrkB, causing the autophosphorylation of TrkB, thereby activating the mitogen-activated protein kinase (MAPK) pathway, the phospholipase C-gamma (PLC-γ) pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and other signaling pathways (42). Finally, CREB is activated at the Ser133 site of the cAMP response element binding protein (CREB). CREB promotes the survival of nerve cells and increases synaptic plasticity and neurogenesis by boosting the expression of the BDNF and BCL-2 genes (43). BDNF-TrkB not only affects the survival, development, and functions of neurons but also promotes the formation of the dendritic spine, provides a structural basis for synapse formation and improves the transmission efficiency of synapses. BDNF/TrkB signaling has a major impact on the production of antidepressant effects (44). Knock-out of the BDNF gene or the reduction of the levels of BDNF in the forebrain blocks the behavioral effects of antidepressants (45). In recent years, more and more studies have found that antidepressants might play an anti-depressant role by up-regulating brain BDNF levels or activating TrkB receptors. Song et al. found that silibinin mitigated the depression-like symptoms of Ap1-42-treated rats by decreasing the BDNF/TrkB expression, suggesting the role of the BDNF/TrkB signaling pathway in the activity of antidepressants (46). Likewise, sesquiterpenoids from
The role of BDNF in depression. Arrows indicate activation; T-shaped arrows indicate inhibition. Akt, serine/threonine protein kinase; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; CaMK, calcium-calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; IP3, inositol 1,4,5-trisphosphate; MEK, mitogen-activated extracellular signal-regulated kinase; PKC, protein kinase C; PI3K, PI-3 kinase; PLC-γ, phospholipase-Cγ; RSK, ribosomal S6 kinase; TrkB, tyrosine kinase B.

ginseng root treatment, ameliorate depression-like behaviors induced by LPS by upregulating the BDNF/TrkB Pathway (47). The BDNF-TrkB pathway in the nucleus accumbens of α7 nACHR knockout mice was demonstrated to be up-regulated, which was considered to be involved in their depression-like behavior (48). The antidepressant role of fisetin was confirmed by Wang et al. which was achieved by activating TrkB rather than regulating its overall level (49). All of these studies suggest that BDNF and the mediated TrkB signaling pathway may provide new approaches for the treatment of depression.

The N-methyl-D-aspartic acid receptor (NMDA receptor) is associated with depression. NMDA receptor antagonism has a significant antidepressant effect. On the one hand, it exerts its antidepressant effect by inhibiting NMDA receptors, which not only promote the establishment of new synaptic connections but also restore the synaptic connections caused by stress damage. On the other hand, antagonizing the NMDA receptor also activates the AMPA receptor, which provides a fast antidepressant effect through its signaling pathway. This provides a new method in the treatment of traditional depression (50). BDNF may play a role through the NMDA receptor. BDNF enhances the AMPA-dependent synaptic signaling in the hippocampus through downstream pathways mediated by NMDA receptors (51). Wang et al. enhanced the BDNF/TrkB signaling pathway by means of transcranial magnetic stimulation (TMS). At the same time, the activity of the NMDA receptor in the cerebral cortex was strongly correlated with the degree of TrkB activation (52). In cultured hippocampal neurons and rat neocortical cells, the activation of TrkB or chronic administration of BDNF can enhance the expression of the NMDA receptor NR1 and NR2A/2B through transcriptional activation. BDNF can also promote the release of glutamate through the presynaptic receptor signal transduction pathway, and enhance the AMPA receptor and NMDA through the postsynaptic receptor pathway and then participate in and promote the formation of LTP (53). Duncan et al. through a study of 30 depressive patients treated with ketamine, found that the antidepressant effect of ketamine might be due to the enhancement of inter-synaptic communication by BDNF (54).

Effects of Antidepressants on BDNF
In recent years, the major clinical antidepressants are monoamine oxidase inhibitors, tricyclic inhibitors, and tetracyclic inhibitors (55, 56). Some clinical studies suggest that antidepressant therapy for a period of time could reverse the decrease of peripheral BDNF levels of depressed patients. Serum BDNF levels of depressed patients taking SSRIs were markedly higher than that of the control group and depressed patients not taking SSRIs (57). Treatment with venlafaxine or paroxetine also increased BDNF in patients with depression (58). However, whether all antidepressants affect BDNF levels, remains controversial. A meta-analysis showed that the level of peripheral BDNF increased during antidepressant treatment of SSRIs and SNRIs, among which sertraline could improve the BDNF level after short-term treatment (59). Treatment with fluoxetine (SSRI) was found to alter BDNF levels in patients with depression, whereas venlafaxine did not (60). Freire et al. found that neither the combined group, nor the pharmacological group resulted in the increase of the serum BDNF level in patients with...
depression, although both significantly improved the depressive symptoms of patients (61). These studies indicate that different antidepressants may have different effects on the peripheral BDNF during treatment.

NEURO-IMMUNE AXIS AND MOOD DISORDERS

Neuro-Immune Axis

Nowadays, plenty of research has been conducted on the interaction between the central nervous system and immune system. It is neurogenic inflammation that determines whether the immune response is caused by a local threat, through the connection of nerve fibers to immune cells. In recent research, a CNS with complicated innate immune responses is demonstrated to have high immunocompetence (62). Microglia, resident immune cells within the brain parenchyma, can secrete some soluble factors, such as chemokines, cytokines, and neurotrophic factor, to adjust the CNS immune response and tissue repair (63). In addition, astrocytes also play an essential role in central immunity. They respond to an inflammatory environment not only in an immunological way by changing their cell phenotype, but also modulate the immune response of lymphocyte in the brain by releasing associated protein molecules, like chemokines and cytokines (64).

Some immune cells, such as non-specific leucocytes and lymphocytes, produce neurotransmitters and neuropeptides. Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45). Opioids may serve as an example. It is suggested that opioids are secreted in inflammatory tissues and act to alleviate clinical pain (45).

Cytokines and Depression

In recent years, studies have found that immune dysfunction was closely related to depression, and pro-inflammatory cytokines produced by innate immune activation were especially closely related to the occurrence and development of depression. Therefore, the hypothesis of cytokine is gradually proposed. The cytokine hypothesis suggests that depression is an inflammatory disease caused by neuroimmune regulation disorders, emphasizing that the body's immune system plays an important role in depression. Cytokines are intercellular information transfer molecules, which mainly have immunomodulatory and multiple effector functions. Different cytokines play different roles in inflammation. Some have proinflammatory effects, while others have anti-inflammatory effects. For instance, IL-1β, IL-6, and tumor necrosis factor α (TNF-α) are relatively advanced proinflammatory cytokines, while IL-4 and IL-10 is the main area of research in anti-inflammatory cytokines. Clinical studies have shown that patients with depression were often associated with varying degrees of inflammatory activation or increased inflammatory molecules, suggesting that the occurrence of depression might be closely related to cytokines (73, 74).

Studies About Cytokines in Depression

This hypothesis has been supported by a large number of clinical cases in recent years: patients with autoimmune diseases and chronic viral infections often showed depressive symptoms (75, 76). Autopsy studies have found that cytokines were significantly increased, as well as the synthesis of carbon monoxide synthase in macrophages, microglia, and astrocyte (77). A number of studies have indicated that various cytokines, such as IL-1β, IL-2, IL-6, TNF-α, and IFN-γ in serum or plasma of patients with depression were significantly increased (78). The results of the meta-analysis showed that the levels of inflammatory factors in patients with depression, including IL-1, IL-6, and TNF-α, were significantly higher than those of healthy people and in positive relevance to the serious extent of depressive symptoms (79–81), and antidepressants could lower these cytokines in people with depression (82). According to the study of the cytokine overview, Zou et al. found that the expression of IL-1, IL-10 and TNF in MDD patients increased significantly, while the expression of IL-8 decreased significantly. Such aberrant changes in the levels of inflammatory cytokines demonstrated that it is depression that activates the inflammatory process (83). Animal studies have also shown that the levels of IL-1β, IL-6, and TNF-α in the brain increased significantly after lipopolysaccharide treatment, as well as depressive behaviors, such as sleep disorders, loss of pleasure, and insufficiency of power (84). Depressive behaviors of animals were blocked after injecting IL-1 receptor antagonist IL-1Ra into animals before stress (85). The results suggested that inflammatory pathways might be involved in the development of depression.

Actions of Cytokines in Depression

People realize that there is a two-way effect between immunity and nerves. Both physiological and psychological stress can activate the immune system and make the cytokines secreted, and then influence the central nervous system, such as...
neurogenesis, neurotransmitter level, neuroendocrine function, neuroplasticity, and behavior related neural pathways (86–88). It leads to changes in the neurochemistry and endocrinology associated with depression and influences the development of depression. Cytokines can promote oxidative stress and damage glial cells in emotionally related brain regions, such as the prefrontal cortex and amygdala (89). In addition, dysfunctions of glutamate-induced by cytokine can reduce the generation of neurotrophic factors (88). Under stress, the increase of proinflammatory cytokines in the human body activates the indolamine 2,3- dioxygenase (IDO), an enzyme that can directly act on the metabolism of tryptophan (TRP). IDO can increase the level of kynurenine produced by TRP metabolism, thereby reducing the level of 5-HT and promoting the occurrence of depression (90). Cytokines are also momentous to the dysfunction of the HPA axis. They induce the hyperactivity of the HPA axis to increase the glucocorticoid for a long time, and the abnormal glucocorticoid signal can affect the production, maintenance, and development of depressive behaviors (91). At the same time, these cytokines and excess glucocorticoids also inhibit nerve regeneration in the brain. Cytokine signaling pathways, for example NF-kB, can disrupt the function and expression of glucocorticoid receptors, leading to an unrestricted inflammatory response, further exacerbating depressive symptoms (92). Additionally, cytokines can also contribute to depression by influencing neural plasticity. Ben et al. confirmed that IL-1 could inhibit neuronal regeneration, and inflammatory cytokines—IL-6, as an example, could disrupt neuronal function (93). Currently, though the causal relationship between cytokines and depression is still considered controversial, it is undeniable that the negative regulation of neuroplasticity in the brain has a significant impact on the developmental progress of depression. Furthermore, the study also shows that abnormally changed levels of cytokines are associated with an increased risk of delirium and suicide (94–96).

**Immune Regulation and Antidepressant Effects**

Some anti-inflammatory drugs have antidepressant effects or enhance antidepressant effects. Studies have shown that the anti-inflammatory drug COX-2 inhibitors could directly or indirectly affect the 5-HT system through the CNS and play an antidepressant effect. Giving rats a dose of rofecoxib can increase the level of 5-HT in the prefrontal and parietal cortex (97). Celecoxib in depressed rats was found to decrease cytokine levels and improve behavior in the hypothalamus (98). Through the drug combinations of celecoxib with antidepressants, such as reboxetine, fluoxetine, and sertraline, it was found that the combined group was better than an antidepressant alone in patients with depression (99–101). Etanercept, a kind of tumor necrosis factor (TNF-α) antagonist, also has a strong antidepressant effect, which can improve depression symptoms and patient fatigue (102). Many other clinical cases show that antidepressants can reduce proinflammatory cytokines and other inflammatory markers in patients (103). Tricyclic antidepressants, SSRI, SNRI, and other antidepressants have been shown to increase anti-inflammatory immunomodulatory cytokine levels by inhibiting inflammatory cytokines and th1-like cytokines (such as IFN-γ). Réus et al. revealed that imipramine, an antidepressant, could reduce the levels of TNF-α and IL-1β in cerebrospinal fluid of maternally deprived adult rats (104). Studies have shown that some non-pharmacological treatments can also improve depressive symptoms by regulating immune inflammatory pathways. Kim et al. believe that acupuncture can reduce the levels of peripheral and central proinflammatory factors (IL-1, IL-6, TNF-α) and proinflammatory neuropeptides, and the results are better in the treatment of depression (105). In addition, exercise can play a synergistic role by inhibiting the immune and inflammatory pathways (106).

**BDNF, NEUROIMMUNE AXIS, AND MOOD DISORDERS**

BDNF is a relatively mature neurotrophic factor, which can promote the proliferation of neurons and glial cells in the inflammation of the nervous system through various molecular mechanisms (107, 108). Glial cells are innate immune cells in the center. They not only synthesize and release multiple inflammatory mediators but also express many inflammatory mediator receptors on the cell surface. Microglia, the first line of defense for the central immune response, exerts essential influence on the inflammatory response in the brain (109). Although there is no direct evidence that microglia are correlated with the nosogenesis of depression, many studies have examined if there is a significant increase in the amount of microglia in the brain in patients with suicidal depression. A previous study observed microgliosis in the dorsolateral prefrontal cortex, anterior cingulate cortex, mediodorsal thalamus, and hippocampus of suicidal patients (110). Torres-Platas et al. also observed a relative increase of primed microglia in depressed suicides (77). Microglia can regulate the release of BDNF. Microglia may take effect on pathogenesis by reducing BDNF expression as well as its high-affinity receptor TrkB. Studies demonstrated that microglia was of extensive and diverse importance for the formation of appropriate synaptic connections during development and maturation, which were frequently mediated by BDNF (111). In addition, high levels of IL-6, IL-1β, and BDNF in LPS-stimulated normal human astrocytes (NHAs) was observed, using an LPS-induced in vitro injury model of astroglial cultures. Vice versa, BDNF can promote the growth of astrocytes and regulate the viability and proliferation of LPS-induced NHA through the PI3K/AKT pathway (112, 113).

Reports repeatedly demonstrated that inflammatory cytokines affect neuronal development as well as apoptosis (114, 115). As a matter of fact, stress and its associated activation of inflammatory cytokines might have a negative effect on neurogenesis and neuroplasticity (84, 116, 117). Considerable research efforts have been devoted to the effect of inflammation on the BDNF expression in the brain. The significant reduction in BDNF was caused by the administration of pro-inflammatory cytokines or lipopolysaccharide (LPS), an inducer for cytokines, serve as an example. LPS injections could significantly reduce mature BDNF levels in the hippocampus and cerebral cortex (118), as well as IFN-α administration, which decreased systemic BDNF levels.
Furthermore, other neurotrophic factors also decreased to varying degrees: NGF and neurotrophic factor-3 (NT-3), for instance (120).

It was demonstrated in a number of research studies that inflammation inhibits BDNF/TrkB expression. Inflammatory cytokines influence the phosphorylation of the BDNF receptor (TrkB), thereby further interfering with BDNF signaling (121). Gibney et al. found that poly-I:C administration upregulated the expression of the inflammatory cytokines, which caused the occurrence of an inflammatory reaction. At the same time, BDNF and TrkB expression in the hippocampus and cortex were downregulated, which might lead to behavioral defects of depression and anxiety (122). In addition, it is under integrated BDNF signaling that antidepressants are able to reverse LPS-induced apoptosis, which agrees well with the above-mentioned studies.

The anti-inflammatory mechanism of antidepressive agents has not been elucidated yet. Imipramine has been shown to suppress proinflammatory cytokines in rat neural stem cells, stimulating the expression of BDNF (123). Studies have shown that the production of inflammatory cytokines was regulated by complex signaling pathways, especially the nuclear factor-κB (NF-κB) inflammatory response signal pathway (BDNF-TrkB-MEK-ERK-NF-κB pathway) whose activation plays a central regulatory role in the inflammatory response. Investigation of the effect and potential mechanism of salidroside on depression showed that salidroside could down-regulate the expression of BDNF, TrkB, and the NF-κB protein (124). Ge et al. thought that the antidepressant effect of resveratrol is mainly to reduce the expression of inflammatory cytokines and improve NF-κB activation (125). Chrysophanol could inhibit the NF-κB signaling pathway (126), and the high dose of fisetin could regulate the expression of NF-κB in the hippocampus to antagonize the expression of iNOS mRNA (127). Similarly, the antidepressant effect of aesculetin may be achieved by inhibiting the NF-κB pathway as well as activating BDNF/TrkB signaling (128). Furthermore, as an inflammatory intracellular signaling molecule, p38 mitogen-activated protein kinase is now a target for clinical studies of chronic inflammatory diseases due to the potential antidepressant effects of its inhibitors (129). All these studies provide a basis for the development of new clinical antidepressants and the continued development of antidepressant treatments.

**CONCLUSION**

Based on many clinical and basic research studies, a variety of theories were proposed to expound the nosogenesis of mood disorders, especially depression. In this review, the neuroimmune axis has been related to mood disorders (Figure 2). BDNF is thought to be involved in the neuroimmune axis regulation. On the one hand, the expression of BDNF is affected by immune cells and the immune factors they secrete. On the other hand, the immunomodulatory process also requires the regulation of BDNF-mediated signaling pathways. Unfortunately, the specific mechanism of how BDNF participates in the regulation of the neuroimmune axis in mood disorders is still unclear and it is therefore necessary to conduct more in-depth research. The treatment of mood disorders in the past often only focus on a certain aspect of research. The characteristics of the varied symptoms of depression determine that these treatments are not effective. Exploring a treatment strategy for depression based on neuroimmune axis regulation may be more helpful to further guide the development of anti-mood disorders drugs.

**AUTHOR CONTRIBUTIONS**

YJ and RJC contributed conception and design of the review. WY organized the documents. YJ wrote the first draft of the manuscript. SBX and LHS wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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