



RESEARCH ARTICLE

The Role of Neuroinflammation and Inflammatory Biomarkers in Major Depressive Disorder

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ABSTRACT

Neuroinflammation plays a significant role in the pathophysiology and progression of major depressive disorder. Elevated levels of inflammatory markers are associated with treatment resistance to conventional antidepressants and poor prognosis. Targeting inflammation with alternative anti-inflammatory treatments might be a promising treatment strategy for patients suffering from depression with underlying immune dysfunction. The use of inflammatory biomarkers is very useful to identify patients with inflammatory abnormalities at risk to develop treatment resistance and to select the appropriate treatment option from the beginning. The aim of the present review is to elucidate the impact of neuroinflammation on the pathogenesis and progression of major depressive disorder. It provides insight into alternative therapies targeting inflammatory pathways, such as electroconvulsive therapy and ketamine, and illustrates the role of potential inflammatory biomarkers to improve prevention of treatment resistance and treatment strategies.

Keywords: Major depressive disorder, neuroinflammation, treatment resistance, immune dysfunction, inflammatory biomarkers.

1. The role of inflammation in major depressive disorder

Major depressive disorder (MDD) is a serious and multifactorial mental illness with a complex pathophysiology, involving immune dysfunction and inflammatory abnormalities. There is evidence that more than a third of patients suffering from MDD do not respond sufficiently to conventional antidepressants and become treatment resistant ¹. Treatment resistant depression (TRD) goes along with increased depression severity, a significant impairment in functioning, higher rates of metabolic and psychiatric comorbidities, and suicidal behavior ^{2,3}.

It is well established that MDD is often associated with elevated levels of peripheral inflammatory markers ⁴⁻⁹ that might correlate with depression severity and treatment resistance ¹⁰⁻¹².

There is evidence for central effects of peripheral inflammation through microglial activation ¹². Microglia are resident immune cells of the brain and can be activated by stress, infection, and chronic systemic inflammation ^{13,14}. Microglial activation leads to an overproduction of pro-inflammatory cytokines, triggering the activation of the enzyme indoleamine-2,3-dioxygenase (IDO), which stimulates the kynurenine pathway that represents the major route for tryptophan metabolism ¹⁵⁻¹⁷. Elevated levels of inflammation also lead to the activation of the hypothalamic-pituitary adrenal axis (HPA-axis) that plays a crucial role in the stress response, stimulating an increased glucocorticoid release ¹⁸⁻²⁰. These pathophysiological mechanisms might cause a dysregulation of serotonergic and noradrenergic systems and contribute to the pathogenesis of MDD. Chronic activation of the HPA-axis and consistently high cortisol concentrations might also have metabolic side effects, including increased appetite and insulin resistance, contributing to the development of obesity and type 2 diabetes (T2D) ²¹.

A diverse profile of peripheral inflammatory markers and metabolic comorbidities might reflect a biological difference among patients suffering from MDD and lead to a different course of illness and treatment response ^{10,11,22}. This subgroup of patients might be affected by an inflammatory cytokine-associated subtype of MDD with a higher risk of metabolic comorbidities, and treatment resistance.

The effect of activated microglia and HPA-axis dysfunction on neurogenesis might be disruptive by triggering neuronal apoptosis and oxidative stress that results in neuroinflammation and cellular damage ^{23,24}. Numerous neuroimaging studies demonstrated that chronic peripheral inflammation and alterations of the HPA-axis might be related to a reduction of cortical gray matter and subcortical volumes as well as impairments of white matter integrity within brain regions that are implicated in the pathophysiology of MDD ²⁵. Mounting evidence revealed an association of MDD with reduced hippocampal volumes due to inflammatory abnormalities and immune dysfunction ^{23,24,26,27}.

Therefore, neuroinflammation and immune dysfunction are strongly implicated in the pathophysiology of MDD, and particularly in the development of TRD.

2. The use of inflammatory biomarkers in major depressive disorder

Given the strong relationship between inflammation and depression, the use of inflammatory biomarkers might be very promising to optimize depression treatment. They can help to distinguish between different subtypes of depression and identify patients who are at risk to develop treatment resistance. Inflammatory biomarkers are very useful to identify patients who might not respond to conventional antidepressants and make it possible to select the appropriate treatment option right from the start. A biomarker-guided treatment enables more personalized treatment strategies to tailor the therapy right to the individual profile of the patient for achieving the best possible treatment results.

Pro-inflammatory cytokines are small signaling proteins, released by immune cells, such as macrophages and lymphocytes, that promote inflammation. Key pro-inflammatory cytokines include interleukin (IL)-6, IL-1 β , tumor necrosis factor (TNF)- α , and interferon (IFN)- γ . They are involved in cell signaling and play a crucial role in the regulation of the inflammatory response. They contribute to various immune processes and are very important for the balance of the immune system. The C-reactive protein (CRP) is an acute-phase protein synthesized primarily in the liver in response to inflammation. It is a valuable indicator of inflammation that is used in healthcare for identifying and monitoring inflammatory processes and can be utilized as a biomarker of inflammation to predict antidepressant response ²⁸. It is a pragmatic and inexpensive option for biomarkers and is measured through commercial laboratories. The pro-inflammatory cytokines IL-6 and TNF- α are more specific and have a high potential to predict antidepressant response, especially in TRD ²⁸. Moreover, IL-6 and TNF- α levels might be associated with depression severity and clinical improvement after treatment ^{11,29}.

3. Inflammatory markers as predictors of antidepressant response

3.1 ANTIDEPRESSANTS

The most common prescribed antidepressants are selective-serotonin reuptake inhibitors (SSRIs) that work by blocking the serotonin (5HT) transporter to increase the availability of serotonin in the synaptic cleft. They might have some anti-inflammatory properties, as the 5-HT system is also involved in inflammation regulation.

Mounting evidence suggests that TNF- α is a key pro-inflammatory cytokine in the development and course of MDD. A major part of patients suffering from MDD have elevated TNF- α levels, and antidepressant treatments might lead to a decrease of TNF- α levels ^{30,31}. A study that examined the relationship between plasma cytokine levels and response to SSRI treatment showed that a decrease of TNF- α levels was associated with an improvement of depressive symptoms after treatment with fluoxetine ³². A recent meta-analysis revealed that

antidepressant treatment might lead to a significant reduction of TNF- α levels correlating with a clinical improvement of depressive symptoms and that responders had a significantly higher reduction of TNF- α levels than non-responders¹¹. Another recent study showed that 12 weeks of antidepressant treatment led to a significant improvement of depressive symptoms that was associated with a decrease in TNF- α levels³¹. Thus, TNF- α might be a potential predictor of treatment response to commonly used antidepressants, such as SSRIs, in individuals with MDD.

There is evidence that tricyclic antidepressants (TCAs) that interact with multiple neurotransmitter systems represent the class of antidepressants with the strongest anti-inflammatory properties by affecting various inflammatory pathways^{33,34}. Treatment with TCAs, such as amitriptyline and imipramine, leads to a modulation of toll-like receptor signaling as well as a reduction of oxidative stress and the production of pro-inflammatory cytokines, including IL-6, TNF- α , IL-1 β , and IL-18³⁴. Therefore, TCAs have been proposed as a potential therapy for atherosclerosis in patients with MDD³⁴.

However, there are studies indicating that antidepressants might not always have an impact on inflammatory blood marker levels and that changes in pro-inflammatory cytokine levels might be independent of antidepressant treatment outcome.

A recent study that investigated the effect of sertraline on cytokine levels in adolescents with first episode MDD indicated significantly higher levels of IL-1 β and IL-6 as well as significantly lower TNF- α levels in adolescents with MDD than in healthy controls³⁵. After 8 weeks of treatment with sertraline, IL-1 β and IL-6 levels decreased and TNF- α levels increased in adolescents with MDD compared to pre-treatment levels. There was only a weak correlation between IL-6 levels and depression severity and not enough support to consider it a potential predictor of treatment response. There was no significant association of baseline IL-1 β and TNF- α levels with clinical response³⁵. A meta-analysis, comprising 32 studies, showed a significant decrease of IL-1 β levels only after SSRI treatment and no significant effect of antidepressants on IL-2, TNF- α , IFN- γ and CRP levels³⁶. A meta-analysis, including 22 studies, revealed that SSRIs induced a decrease of IL-6 and TNF- α levels. However, the use of other antidepressants, though effective on depressive symptoms, had no impact on cytokine levels³⁷. A plenty of studies indicated a significant reduction of IL-6 levels due to antidepressant treatment and no significant correlation with depression severity^{10,38}.

3.2 ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is a highly effective and fast-acting treatment for a multitude of mental illnesses, including severe depression and TRD^{39,40}. It is well known that ECT leads to a modulation of neurotransmitter levels, neurogenesis, and inflammatory cytokine levels^{41,42}.

There is evidence from meta-analyses that ECT leads to a significant brain volume increase in limbic structures, such as the hippocampus and the amygdala, compared

to pre-treatment values in patients with MDD^{43,44}. However, the relationship between these volumetric changes and clinical improvement of depressive symptoms following ECT needs further investigation^{43,44}.

Mounting evidence indicates that patients with MDD and elevated levels of peripheral inflammation are more likely not to respond to conventional antidepressants and benefit more from anti-inflammatory treatments, including ECT^{10,45,46}. Several studies have examined whether levels of inflammatory markers before treatment might predict response to ECT.

A very recent meta-analysis revealed that higher IL-6 and CRP baseline levels were significantly related to a greater improvement of depressive symptoms over the course of ECT⁴⁷. Kruse et al. (2018)⁴⁸ indicated that higher IL-6 levels before ECT were associated with a greater reduction of depressive symptoms, identifying those depressed patients most likely to benefit from ECT. A recent study by Du et al. (2024)⁴⁹ showed that ECT was effective in treating severe MDD in adolescents and that clinical improvement was associated with a decrease in IL-6 levels. There is evidence that ECT exerts an acute effect on inflammatory cytokine levels, particularly on IL-6 levels, leading to a rapid increase after the first sessions and a long-term effect inducing a decrease of IL-6 levels over the course of treatment in ECT responders^{48,50-52}. The long-term effect of ECT on IL-6 levels might be associated with treatment outcome, highlighting its potential role as a biomarker of ECT response in patients with MDD^{48,50,51}.

However, there are studies indicating no relationship between changes in levels of inflammatory markers and of ECT outcome. A prospective study revealed no significant difference between IL-6 levels before and after ECT, and the alterations in other pro-inflammatory cytokine levels were not related to treatment response in patients with TRD⁴¹. Furthermore, Rush et al. (2016)⁵³ showed elevated baseline IL-6 levels that did not normalize after ECT completion and were not associated with clinical response in patients with MDD.

3.3 KETAMINE

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is an anesthetic drug with analgesic, anti-inflammatory, and antidepressant effects⁵⁴⁻⁵⁷. Ketamine functions by blocking the transmission of glutamate at the NMDA receptor. Ketamine has diverse properties and might exert its therapeutic effects through anti-inflammatory actions on the HPA-axis and the kynurenine pathway⁵⁸. The administration of ketamine might also exert rapid antidepressant effects in patients with TRD by inducing a fast increase in brain-derived neurotrophic factor (BDNF) levels⁵⁹ that plays a crucial role in neuronal growth and represents an important marker of neuroplasticity⁶⁰.

Repeated ketamine administration has a modulating effect on hippocampal neurogenesis⁶¹. A recent study showed that the treatment with ketamine led to a significant reduction of depressive symptoms, an increase of right hippocampal volume, and changes in inflammatory marker levels⁶². Hippocampal volume increase was not associated with alterations in

inflammatory markers, indicating a complex neurobiological mechanism of the antidepressant effect of ketamine ⁶².

A growing body of evidence indicates that ketamine induces a rapid reduction of depressive symptoms correlating with changes in inflammatory cytokine levels in patients with TRD ^{55,63,64}. A double-blind randomized controlled trial showed that the reduction in TNF- α levels 40 minutes post-infusion correlated positively with a decrease in depressive symptoms ⁶³. Moreover, a higher baseline inflammatory state might be associated with a better response to ketamine ⁶³. A recent study by Zhan et al. (2020) ⁶⁴ revealed a downregulation of plenty of inflammatory markers during ketamine treatment and

that changes in levels of IL-6 and IL-17A were associated with an improvement of depressive symptoms.

However, there are also studies indicating no correlation between changes in inflammatory cytokine levels and clinical improvement after ketamine treatment ^{65,66}, suggesting that inflammatory cytokines might be unreliable biomarkers of the antidepressant response to ketamine ⁵⁵.

Table 1 gives an overview of studies supporting the potential of inflammatory markers as predictors of treatment response to antidepressants, ECT, and ketamine, and of studies showing no significant association between blood levels of inflammatory markers and treatment response.

Table 1: Inflammatory markers as predictors of response to antidepressants, ECT, and ketamine (meta-analysis / systematic review)

Blood levels of	CRP	IL-6	TNF- α
Predictor of treatment response to Antidepressants	Yin et al. 2025 ²⁹ ; Uher et al. 2014 ⁶⁷	Yin et al. 2025 ²⁹ ; Carboni et al. 2019 ⁶⁸ ; Goldsmith et al. 2016 ⁶⁹ ; Dahl et al. 2014 ⁷⁰ ; Yoshimura et al. 2009 ⁷¹ ; Leo et al. 2006 ⁷²	Liu et al. 2020 ¹¹ ; Yao et al. 2020 ³¹ ; Carboni et al. 2019 ⁶⁸ ; Strawbridge et al. 2015 ¹⁰ ; Fornaro et al. 2013 ⁷³ ; Leo et al. 2006 ⁷²
No significant association with treatment response to Antidepressants	Wiedlocha et al. 2018 ³⁶	Xiang et al. 2023 ³⁵ ; Köhler et al. 2018 ⁷⁴ ; Hannestad et al. 2011 ³⁷	Xiang et al. 2023 ³⁵ ; Wiedlocha et al. 2018 ³⁶ ; Köhler et al. 2018 ⁷⁴ ; Hannestad et al. 2011 ³⁷
Predictor of treatment response to ECT	Dellink et al. 2025 ⁴⁷ ; Carlier et al. 2019 ⁴⁶	Dellink et al. 2025 ⁴⁷ ; Du et al. 2024 ⁴⁹ ; Kruse et al. 2018 ⁴⁸ ; Freire et al. 2017 ⁷⁵ ; Järventausta et al. 2017 ⁵⁰	Sorri et al. 2018 ⁷⁶ ; Pinna et al. 2018 ⁷⁷
No significant association with treatment response to ECT		Zincir et al. 2016 ⁴¹ ; Rush et al. 2016 ⁵³	Zincir et al. 2016 ⁴¹
Predictor of treatment response to Ketamine		Wang et al. 2024 ⁷⁸ ; Zhou et al. 2021 ⁷⁹ ; Zhan et al. 2020 ⁶⁴ ; Chen et al. 2018 ⁶³	Wang et al. 2024; Chen et al. 2018 ⁶³
No significant association with treatment response to Ketamine		Kiraly et al. 2017 ⁶⁵ ; Park et al., 2017 ⁶⁶	Kiraly et al. 2017 ⁶⁵ ; Park et al., 2017 ⁶⁶

4. Conclusion

Immune dysregulation is a crucial contributing factor to the development of MDD. Inflammatory alterations might affect monoamine systems and brain structures, leading to neuroinflammation and long-term neuronal damage and dysfunction ^{23,24}. Therefore, it is of great importance to identify patients with an inflammatory subtype of MDD early in the course of illness to prevent treatment resistance and chronification of depression. The use of inflammatory biomarkers is a highly beneficial method for selecting the appropriate treatment option and achieving a rapid treatment response.

As previously described, patients with MDD and elevated levels of pro-inflammatory cytokines have a poorer response to conventional antidepressants ^{10,32}. A potential biomarker of antidepressant response to conventional antidepressants, such as SSRIs, might be TNF- α . However, there are numerous studies denying the reliability of inflammatory biomarkers in predicting treatment response to antidepressants.

A growing body of evidence suggests that depressed patients with higher levels of inflammatory markers might benefit more from alternative treatments with an anti-

inflammatory mechanism, such as ECT and ketamine ^{10,45,46}. Both ECT and ketamine lead to a fast reduction of depressive symptoms that is associated with changes in cytokine levels in patients with TRD ^{52,55,63,64}. Mounting evidence indicates that the most promising biomarker of antidepressant response to ECT ⁴⁸⁻⁵¹ and ketamine ^{64,78,79} might be IL-6. Although there are a few studies questioning the reliability of pro-inflammatory cytokines as biomarkers of antidepressant response to ketamine and ECT, studies that support their potential as biomarkers of treatment response are clearly prevailing.

There is a need for conducting further studies with higher sample sizes to examine the use of potential

inflammatory biomarkers in the clinical assessment of patients with MDD to better guide treatment selection and obtain the best possible treatment outcome.

5. Conflicts of interest statement

The author declares no conflicts of interest.

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