



Review

INFLAMMATION AND DEPRESSION: THE INVOLVEMENT OF CYTOKINES

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ABSTRACT

Major depressive disorder (MDD) is a frequent, debilitating psychiatric condition characterized by low mood and functional burden. It is a heterogeneous disorder, with a complex pathophysiology that includes genetic, environmental, biological, and psychosocial factors. Inflammation is often associated with MDD as well, with elevated levels of proinflammatory cytokines, such as IL-1, IL-6, and TNF, repeatedly presenting in combination with depression. Increasing evidence promotes the “inflammation hypothesis” of MDD, suggesting that acute and chronic inflammation contributes to depression pathophysiology and affects neurological processes. An activated immune response and the release of proinflammatory cytokines could affect neural plasticity, neuroendocrine function, and neurotransmitter metabolism, and ultimately, cytokines could serve as indicators for risk, as well as treatment, of certain subsets of depression.

Keywords: *Depression; Major depressive disorder; Inflammation; Cytokines; IL-1; IL-6; TNF; Immunity; Neurological disease*

INTRODUCTION

Major depressive disorder (MDD) is a frequent and disabling psychiatric condition and public health issue that is characterized by low mood and functional burden. The World Health Organization describes depression as “sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration” (1). As of 2015, it was estimated that 322 million people worldwide were living with depression (1). It is one of the primary causes of worldwide disability and has a high lifetime prevalence rate (2). MDD can have symptoms ranging from mild to severe, can be periodic or long-lasting, and can severely impair the functioning of daily life for an individual. In addition, sufferers have a higher risk of suicidality, and ultimately, suicide (3).

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MDD is a heterogeneous disorder with a complicated pathophysiology, involving environmental and hereditary factors, and increasing evidence implicates the involvement of the immune system. Proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) are seen at increased levels in MDD (4) and are associated with the occurrence of depression-like symptoms (5). Immune activation and the subsequent continual release of proinflammatory cytokines can raise cortisol levels by affecting the hypothalamic–pituitary–adrenal (HPA) axis (6–7). Chronic stress can lead to continual elevation of cortisol levels and desensitization of glucocorticoid receptors, resulting in decreased hippocampal neurogenesis (8).

As biomarkers, proinflammatory cytokines such as IL-1, IL-6, and TNF, may be able to indicate risk for certain subsets of depression and could be useful in therapeutic treatment (9). In addition, inhibition of proinflammatory cytokine levels could be curative.

Depression Pathophysiology

The monoamine-deficiency theory has been a predominant explanation of depression pathophysiology since the 1950s (10). It posits that a deficiency in levels of neurotransmitters in the central nervous system (CNS), such as serotonin, norepinephrine, and dopamine, is associated with MDD development (11). However, this theory cannot explain the pathophysiology of MDD, as it is a heterogeneous disorder with diverse etiologies, stemming from genetic, environmental, biological, and psychosocial factors. The pathophysiology is complex, likely involving multifactorial mechanisms that work together. In fact, there is a high rate of treatment resistance with antidepressants, between 30–50% (12), which suggests there may be other untargeted factors involved.

Genetic and environmental factors play a role in the development of MDD. There is a familial component, with a proposed 30–40% heritability based on family and twin studies (13). Individual-specific environmental factors such as history of abuse, trauma, relationship problems, and chronic or severe stress, also increase the risk of developing MDD (14–16).

In some studies, volume loss has been observed in brain regions, particularly in the hippocampus, of those with MDD (17–20). Hippocampal atrophy appears to be associated with the length of depression and can be limited with the use of antidepressants (20). However, the etiology of this phenomena is unknown and it has been suggested that stress (21), cortisol elevation, glutamatergic pathways, genetics (22), and increased cellular density may play a role (23–24). Interestingly, as inflammation becomes increasingly suspected in the pathophysiology of MDD, studies have shown an association between inflammatory biomarkers and reduced hippocampal volume (25–26). Environmental stress has been correlated to inflammatory effects, with increased inflammatory markers and loss of volume in the hippocampus (26).

Recently, research has begun to indicate the role of inflammation in MDD pathophysiology, which has led to an “inflammation hypothesis”. It is hypothesized that inflammation may play a central role in the development and persistence of MDD in some subsets of people. Acute and chronic inflammation can affect neurobiological pathways and alter neurocircuitry by decreasing neurotransmitter metabolism and neurogenesis and increasing glutamate excitotoxicity (27).

The inflammatory hypothesis of MDD

The innate immune system initiates acute inflammatory activation in response to foreign pathogens or tissue damage. Microglia are the innate immune cells of the CNS that have functions similar to macrophages. Activated microglia release proinflammatory cytokines, small proteins which regulate cell signaling, mediating immune responses (28). With recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), granulocytes congregate to the site and inflammatory mediators are produced, including cytokines, which are involved in repairing and clearing cell damage. Inflammation can subside after repair and clearance or can become chronic and result in the hyper-activation of cells and sustained production of proinflammatory cytokines, reinforcing the inflammatory state.

Brain-immune interactions may be involved in the development of MDD. The brain and the immune system are connected by neural communication pathways, and proinflammatory cytokines can mediate behavioral effects by acting as neurotransmitters and neuroregulators (29). These behavioral effects are similar to those seen in MDD, as well as those associated with depression in late life and following illness (30).

Chronic inflammation, and abnormal immune activation, is at the base of diverse autoimmune, neurodegenerative, metabolic, and vascular diseases, in addition to cancer (31), and depression following disease is a common occurrence (32). The co-morbidity of illness and depression suggests there is a causal relationship involving the pathophysiological processes of disease, which could be related to inflammation and the involvement of proinflammatory cytokines (29, 33).

The release of inflammatory cytokines such as IL-1, IL-6, and TNF following immune activation causes “sickness behavior” with characteristics similar to depressive-like symptoms, producing fever, malaise, fatigue, and alterations in lipid and protein metabolism (34–35).

Studies have shown that some anti-inflammatory therapies, in combination with conventional antidepressants, improved depressive symptoms in patients (36–37), further implicating the role of inflammation in MDD and suggesting that immune-targeted therapies could be useful in treating the disorder.

Strong evidence indicates that inflammation does play a role in initiating depressive symptoms in certain individuals. Furthermore, the diverse peripheral inflammatory biomarkers observed in MDD, and evidence so far, suggests the possibility of other causal pathways, such as depression causing and maintaining inflammation, inflammation leading to depression, or the combined relationship of both (4). However, further research is necessary to elucidate the relationship between inflammation and MDD.

Cytokines and Depression

An activated inflammatory response causes the release of proinflammatory cytokines, which can access the brain and alter behavior, affecting neural plasticity, neuroendocrine function, and neurotransmitter metabolism (38). Studies have shown that MDD is associated with higher circulating C-reactive protein (CRP) concentrations and elevated levels of proinflammatory cytokines such as IL-1, IL-6, TNF, and interferon-gamma (INF- γ) (which increases in viral infection) (4, 39-41). This is in line with replicated reports from other studies, suggesting an inflammatory state accompanying MDD. One study showed that 75% of medically healthy MDD subjects had elevated levels of diverse proinflammatory cytokines, including MCP-1, IL-1 α , IL-1 β , IL-2, IL-6, IL-8, and INF- γ (42). IL-1 and IL-6 are strongly indicated in depression and IL-6 is considered a peripheral biomarker. The combination of IL-6 with other cytokines could be useful for the classification of MDD subtypes and identifying treatment options (9).

Inflammation of the CNS with increased peripheral blood inflammatory biomarkers and elevated levels of proinflammatory cytokines has been seen in individuals with neurodegeneration and depressive symptoms such as sleep disturbances, low mood, fatigue, and anhedonia (41, 43, 44). Increased IL-6 has been linked with sleep deprivation and dysregulation (44, 45). Childhood maltreatment also predicted elevated levels of CRP and IL-6 in adulthood and could be correlated with reduced hippocampal volume (25), although other interindividual factors of vulnerability may likely be involved as well.

Interestingly, both medically healthy and ill patients with MDD show classic features of inflammation, with increased cytokines and other inflammatory markers (46). Treatment with cytokines has been shown to induce mood and cognitive changes similar to those in depression (5). For example, subcutaneous and intravenous injections of IL-2, which is a T-cell growth factor and induces inflammation, were seen to initiate depressive symptoms (47), and TNF administration in mice creates depression-like behavior (48). Interferon- α (IFN- α) is used in therapy for various infectious diseases and cancer, but IFN- α frequently produces depressive-like symptoms, anxiety, anhedonia, and changes in cognitive function (49, 50), to the extent that 20-50% of patients undergoing treatment with IFN- α are diagnosed with depression (51, 52). Interestingly, this IFN- α therapy-induced depressive state improves with antidepressant medication (52). Depression was also seen to be more prevalent following immunotherapy with IL-6, IL-8 and IL-10 (53, 54).

What are the mechanisms by which cytokines could induce depression? Inflammatory cytokines can affect the body's stress-regulation system, affecting the HPA axis. The HPA axis is closely linked to stress and its malfunction is associated with diverse mental diseases, including depression. Glucocorticoids are important for regulating homeostasis during stressful challenges that affect neuroendocrine and immune responses. Proinflammatory cytokines may raise cortisol, which is an anti-inflammatory immunosuppressor, and maintain hypercortisolemia. IL-1 was seen to elevate corticotropin-releasing hormone (CRH), adrenocorticotropic hormone, and corticosteroid levels, activating the sympathoadrenal system and HPA axis. Cytokines can interfere with glucocorticoid receptor signaling and response, which could lead to glucocorticoid resistance and the release of CRH (55), and eventually, decreased hippocampal neurogenesis.

Regarding the classic monoamine theory of MDD, there is evidence supporting cytokine influence on the noradrenergic and serotonergic systems (11) by synthesis, release, and reuptake of different neurotransmitters (56). Animal studies show that cytokine administration affects monoamine metabolism (57), likely via the enzyme indoleamine 2,3 dioxygenase (IDO) in glial cells, which can be activated by cytokines through inflammatory signaling pathways (58). Ultimately, IDO activation is associated with low levels of serotonin (59).

Additionally, in the event of sustained inflammation, cytokines can affect neural plasticity by diverse mechanisms, including decreased neurogenesis, reduced neurotrophic support, glutamatergic activation, apoptosis in astrocytes and oligodendrocytes, and oxidative stress, amongst others (56, 60-62).

Inflammation in depression and oral health

It is clear from a literature review that there is a statistically significant correlation between depression and pathologies of the oral cavity. Specifically, a pathological situation at the level of the oral cavity's immune system can induce depressive symptoms through neuroimmune interactions that are relevant to depression (63,64).

It is clear to date that periodontal disease is a multifactorial pathology that does not only have a bacterial origin, but rather the immune system plays a fundamental role in the etiogenesis (64). Specifically, mast cells appear to mediate the transition between gingivitis and periodontitis through the activation of T lymphocytes and the release of chemokines and cytokines that mediate the destruction of periodontal tissue. In patients with chronic diseases or disabling conditions (65-68), this mechanism is amplified by both internal factors of cytokine dysregulation and external factors such as poor oral hygiene habits due to the limiting pathology. The role of inflammation mediators has now been clarified to the extent that they are targeted by immunomodulatory therapies such as laser or, to a greater extent, photobiomodulation (69).

Some authors point out that the same inflammatory cytokines are involved in periodontal disease and depression and that they have a bidirectional correlation between them.

Therefore, a multidisciplinary approach including the dental team could be useful for patients with depression to improve oral health and thus contribute to the overall improvement of the patient's systemic health. Experimental studies should be carried out to help define a specific protocol for the most common manifestations at the level of the oral cavity of individuals suffering from depression to intercept the pathology early and to provide specific, aimed oral health care.

CONCLUSION

MDD continues to be a public health concern and cause severe impairment for large numbers of individuals around the world. As time progresses, it becomes increasingly apparent that traditional approaches are not sufficient and a unified hypothesis of MDD does not exist, as it is a multi-system, heterogeneous disorder with complex mechanisms of interaction between diverse components (70).

Continuing research suggests the involvement of the immune system in contributing to the pathophysiology of MDD, with repeated studies showing elevations of proinflammatory cytokines in depressed individuals, the majority of which include IL-1, IL-6, and TNF. These cytokines interact with diverse pathophysiological processes involved in depression, leading to the inflammatory hypothesis of MDD. This hypothesis could lead to important findings for the evaluation and treatment of MDD. Inflammatory biomarkers can be useful for identifying subsets of depression and appropriate treatments for these individuals.

Strong evidence has suggested that inflammation is present with depression, likely involved in causation for some individuals. However, the process of inflammation resulting from depression itself must be investigated further. This could describe further mechanisms of the pathogenesis, indicate biomarkers, and improve therapy options.

Conflict of interest

The author declares that they have no conflict of interest.

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