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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, cytokine, 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).

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).

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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 heterogenous 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 is 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-1α, IL-1β, IL-2, IL-6, IL-8, and IFN-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).

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 (63). 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 (64-67), 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 (68).

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.

CONCLUSIONS

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 (69).

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 authors declare that they have no conflict of interest.

REFERENCES

1. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
2. Üstün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJL. Global burden of depressive disorders in the year 2000. *British Journal of Psychiatry*. 2004;184(5):386-392. doi:10.1192/bjp.184.5.386
3. Xin LM, Chen L, Su YA, et al. Risk Factors for Recent Suicide Attempts in Major Depressive Disorder Patients in China: Results From a National Study. *Frontiers in Psychiatry*. 2018;9:300. Published 2018 Jul 3. doi:10.3389/fpsyt.2018.00300
4. Howren MB, Lamkin DM, Suls J. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosomatic Medicine*. 2009;71(2):171-186. doi:10.1097/psy.0b013e3181907c1b
5. Meyers CA. Mood and Cognitive Disorders in Cancer Patients Receiving Cytokine Therapy. *Advances in Experimental Medicine and Biology*. 1999;461:75-81. doi:10.1007/978-0-585-37970-8_5
6. Silverman MN, Pearce BD, Biron CA, Miller AH. Immune Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis during Viral Infection. *Viral Immunology*. 2005;18(1):41-78. doi:10.1089/vim.2005.18.41
7. Gwosdow AR, Kumar MS, Bode HH. Interleukin 1 stimulation of the hypothalamic-pituitary-adrenal axis. *American Journal of Physiology-Endocrinology and Metabolism*. 1990;258(1):E65-E70. doi:10.1152/ajpendo.1990.258.1.e65

8. Saaltink DJ, Vreugdenhil E. Stress, glucocorticoid receptors, and adult neurogenesis: a balance between excitation and inhibition? *Cellular and Molecular Life Sciences*. 2014;71(13):2499-2515. doi:10.1007/s00018-014-1568-5
9. Ting EY, Yang AC, Tsai SJ. Role of Interleukin-6 in Depressive Disorder. *International Journal of Molecular Sciences*. 2020;21(6):2194. doi:10.3390/ijms21062194
10. Freis ED. Mental Depression in Hypertensive Patients Treated for Long Periods with Large Doses of Reserpine. *New England Journal of Medicine*. 1954;251(25):1006-1008. doi:10.1056/nejm195412162512504
11. Delgado, PL. Depression: the case for a monoamine deficiency. *The Journal of clinical psychiatry*. 2000;61(Suppl 6):7-11.
12. Bschor T, Ising M, Erbe S, et al. Impact of citalopram on the HPA system. A study of the combined DEX/CRH test in 30 unipolar depressed patients. *Journal of Psychiatric Research*. 2012;46(1):111-117. doi:10.1016/j.jpsychires.2011.09.020
13. Sullivan PF, Neale MC, Kendler KS. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry*. 2000;157(10):1552-1562. doi:10.1176/appi.ajp.157.10.1552
14. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. *Preventive Medicine*. 2003;37(3):268-277. doi:10.1016/s0091-7435(03)00123-3
15. Beach SR, Fincham FD, Katz J. Marital therapy in the treatment of depression: toward a third generation of therapy and research. *Clinical Psychology Review*. 1998;18(6):635-661. doi:10.1016/s0272-7358(98)00023-3
16. Mazure CM. Life Stressors as Risk Factors in Depression. *Clinical Psychology: Science and Practice*. 1998;5(3):291-313. doi:10.1111/j.1468-2850.1998.tb00151.x
17. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *The American journal of psychiatry*. 2004;161(11):1957-1966. doi:10.1176/appi.ajp.161.11.1957
18. McKinnon MC, Yucel K, Nazarov A, MacQueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience*. 2009;34(1):41–54.
19. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower Hippocampal Volume in Patients Suffering from Depression: A Meta-Analysis. *American Journal of Psychiatry*. 2004;161(4):598-607. doi:10.1176/appi.ajp.161.4.598
20. Sheline YI, Gado MH, Kraemer HC. Untreated Depression and Hippocampal Volume Loss. *American Journal of Psychiatry*. 2003;160(8):1516-1518. doi:10.1176/appi.ajp.160.8.1516
21. MacQueen G, Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research. *Molecular Psychiatry*. 2010;16(3):252-264. doi:10.1038/mp.2010.80
22. Frodl T, Möller HJ, Meisenzahl E. Neuroimaging genetics: new perspectives in research on major depression. *Acta Psychiatrica Scandinavica*. 2008;118(5):363-372. doi:10.1111/j.1600-0447.2008.01225.x
23. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*. 2002;5(11):1242-1247. doi:10.1038/nn958
24. Cobb JA, Simpson J, Mahajan GJ, et al. Hippocampal volume and total cell numbers in major depressive disorder. *Journal of Psychiatric Research*. 2013;47(3):299-306. doi:10.1016/j.jpsychires.2012.10.020
25. Frodl T, Carballedo A, Hughes MM, et al. Reduced expression of glucocorticoid-inducible genes GILZ and SGK-1: high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. *Translational Psychiatry*. 2012;2(3):e88-e88. doi:10.1038/tp.2012.14
26. Mondelli V, Cattaneo A, Murri MB, et al. Stress and inflammation reduce BDNF expression in first-episode psychosis: a pathway to smaller hippocampal volume. *The Journal of clinical psychiatry*. 2011;72(12):1677-1684. doi:10.4088/JCP.10m06745
27. Raison CL, Charles L, Miller AH. Do cytokines really sing the blues? *Cerebrum*. 2013(10).
28. Charo IF, Ransohoff RM. The Many Roles of Chemokines and Chemokine Receptors in Inflammation. *New England Journal of Medicine*. 2006;354(6):610-621. doi:10.1056/nejmra052723
29. Pollak Y, Yirmiya R. Cytokine-induced changes in mood and behaviour: implications for 'depression due to a general medical condition', immunotherapy and antidepressive treatment. The International Journal of Neuropsychopharmacology. 2002;5(4):389-399. doi:10.1017/s1461145702003152
30. Dantzer R, Konsman JP, Bluthé RM, Kelley KW. Neural and humoral pathways of communication from the immune system to the brain: parallel or convergent? *Autonomic Neuroscience*. 2000;85(1-3):60-65. doi:10.1016/s1566-0702(00)00220-4

31. Yao C, Narumiya S. Prostaglandin-cytokine crosstalk in chronic inflammation. *British Journal of Pharmacology*. 2019;176(3):337-354. doi:10.1111/bph.14530
32. Hosaka T, Aoki T, Watanabe T, Okuyama T, Kurosawa H. Comorbidity of depression among physically ill patients and its effect on the length of hospital stay. *Psychiatry and Clinical Neurosciences*. 1999;53(4):491-495. doi:10.1046/j.1440-1819.1999.00580.x
33. Maier SF, Watkins LR. Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review*. 1998;105(1):83-107. doi:10.1037/0033-295x.105.1.83
34. Dantzer R. Cytokine, Sickness Behavior, and Depression. *Immunology and Allergy Clinics of North America*. 2009;29(2):247-264. doi:10.1016/j.iac.2009.02.002
35. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*. 2006;27(1):24-31. doi:10.1016/j.it.2005.11.006
36. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *International Clinical Psychopharmacology*. 2006;21(4):227-231. doi:10.1097/00004850-200607000-00005
37. Müller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Molecular Psychiatry*. 2006;11(7):680-684. doi:10.1038/sj.mp.4001805
38. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depression and Anxiety*. 2013;30(4):297-306. doi:10.1002/da.22084
39. Azar R, Mercer D. Mild Depressive Symptoms Are Associated with Elevated C-Reactive Protein and Proinflammatory Cytokine Levels During Early to Midgestation: A Prospective Pilot Study. *Journal of Women's Health*. 2013;22(4):385-389. doi:10.1089/jwh.2012.3785
40. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in Interleukin-1β in Late-Life Depression. American *Journal of Psychiatry*. 2005;162(1):175-177. doi:10.1176/appi.ajp.162.1.175
41. Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. *Biological Psychiatry*. 2009;65(9):732-741. doi:10.1016/j.biopsych.2008.11.029
42. Simon NM, McNamara K, Chow CW, et al. A detailed examination of cytokine abnormalities in Major Depressive Disorder. *European Neuropsychopharmacology*. 2008;18(3):230-233. doi:10.1016/j.euroneuro.2007.06.004
43. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2005;104(4):788-793. doi:10.1002/cncr.21234
44. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory Markers and Sleep Disturbance in Major Depression. *Psychosomatic Medicine*. 2005;67(2):187-194. doi:10.1097/01.psy.0000149259.72488.09
45. Irwin MR, Wang M, Ribeiro D, et al. Sleep Loss Activates Cellular Inflammatory Signaling. *Biological Psychiatry*. 2008;64(6):538-540. doi:10.1016/j.biopsych.2008.05.004
46. Zorrilla EP, Luborsky L, McKay JR, et al. The Relationship of Depression and Stressors to Immunological Assays: A Meta-Analytic Review. *Brain, Behavior, and Immunity*. 2001;15(3):199-226. doi:10.1006/brbi.2000.0597
47. Capuron L, Ravaud A, Dantzer R. Early Depressive Symptoms in Cancer Patients Receiving Interleukin 2 and/or Interferon Alfa-2b Therapy. *Journal of Clinical Oncology*. 2000;18(10):2143-2151. doi:10.1200/jco.2000.18.10.2143
48. Wen J, Chen CH, Stock A, Doerner J, Gulinello M, Putterman C. Intracerebroventricular administration of TNF-like weak inducer of apoptosis induces depression-like behavior and cognitive dysfunction in non-autoimmune mice. *Brain, Behavior, and Immunity*. 2016;54:27-37. doi:10.1016/j.bbi.2015.12.017
49. Sleijfer S, Bannink M, Gool AR, Kruit WHJ, Stoter G. Side Effects of Interferon-α Therapy. *Pharmacy World & Science*. 2005;27(6):423-431. doi:10.1007/s11096-005-1319-7
50. Fontana RJ, Kronfol Z, Lindsay KL, et al. Changes in Mood States and Biomarkers During Peginterferon and Ribavirin Treatment of Chronic Hepatitis C. *The American Journal of Gastroenterology*. 2008;103(11):2766-2775. doi:10.1111/j.1572-0241.2008.02106.x

51. Capuron L, Gumnick J, Musselman D, et al. Neurobehavioral Effects of Interferon-α in Cancer Patients Phenomenology and Paroxetine Responsiveness of Symptom Dimensions. *Neuropsychopharmacology*. 2002;26(5):643-652. doi:10.1016/s0893-133x(01)00407-9
52. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa. *New England Journal of Medicine*. 2001;344(13):961-966. doi:10.1056/nejm200103293441303
53. Capuron L, Ravaud A, Gualde N, et al. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology*. 2001;26(8):797-808. doi:10.1016/S0306-4530(01)00030-0
54. Bonaccorso S, Puzella A, Marino V, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Research*. 2001;105(1-2):45-55. doi:10.1016/s0165-1781(01)00315-8
55. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, behavior, and immunity*. 2007;21(1):9-19. doi:10.1016/j.bbi.2006.08.009
56. Miller AH, Timmie WP. Mechanisms of Cytokine-Induced Behavioral Changes: Psychoneuroimmunology at the Translational Interface Norman Cousins Lecture. *Brain, behavior, and immunity*. 2009;23(2):149-158. doi:10.1016/j.bbi.2008.08.006
57. Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. *Progress in Neurobiology*. 2008;85(1):1-74. doi:10.1016/j.pneurobio.2008.01.004
58. Fujigaki H, Saito K, Fujigaki S, et al. The Signal Transducer and Activator of Transcription 1α and Interferon Regulatory Factor 1 Are Not Essential for the Induction of Indoleamine 2,3-Dioxygenase by Lipopolysaccharide: Involvement of p38 Mitogen-Activated Protein Kinase and Nuclear Factor-κB Pathways, and Synergistic Effect of Several Proinflammatory Cytokines. *The Journal of Biochemistry*. 2006;139(4):655-662. doi:10.1093/jb/mvj072
59. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience*. 2008;9(1):46-56. doi:10.1038/nrn2297
60. Goshen I, Kreisel T, Ben-Menachem-Zidon O, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Molecular Psychiatry*. 2007;13(7):717-728. doi:10.1038/sj.mp.4002055
61. Ben Menachem-Zidon O, Goshen I, Kreisel T, et al. Intrahippocampal Transplantation of Transgenic Neural Precursor Cells Overexpressing Interleukin-1 Receptor Antagonist Blocks Chronic Isolation-Induced Impairment in Memory and Neurogenesis. *Neuropsychopharmacology*. 2007;33(9):2251-2262. doi:10.1038/sj.npp.1301606
62. Buntinx M, Moreels M, Vandenabeele F, et al. Cytokine-induced cell death in human oligodendroglial cell lines: I. Synergistic effects of IFN-gamma and TNF-alpha on apoptosis. *Journal of Neuroscience Research*. 2004;76(6):834-845. doi:10.1002/jnr.20118
63. Sheethal HS, Kn H, Smitha T, Chauhan K. Role of mast cells in inflammatory and reactive pathologies of pulp, periapical area and periodontium. *J Oral Maxillofac Pathol*. 2018;22(1):92-97. doi:10.4103/jomfp.JOMFP_278_17
64. Tecco S, Sciara S, Pantaleo G, et al. The association between minor recurrent aphthous stomatitis (RAS), children's poor oral condition, and underlying negative psychosocial habits and attitudes towards oral hygiene. *BMC Pediatr*. 2018;18(1):136. Published 2018 Apr 13. doi:10.1186/s12887-018-1094-y
65. Roncati M, Polizzi E, Cingano L, Gherlone EF. An oral health aid for disabled patients. *Dental Cadmos.* 2013;81(7):447 - 452.
66. Parisi MR, Tecco S, Gastaldi G, et al. Point-of-care testing for hepatitis C virus infection at alternative and high-risk sites: an Italian pilot study in a dental clinic. *New Microbiol*. 2017;40(4):242-245.
67. Polizzi E, Tetè G. Manual vs Mechanical Oral Hygiene Procedures: Has the Role of the Dental Hygienist in Phase 2 Post-lockdown Really Changed? *Oral Health Prev Dent*. 2020;18(1):1031-1037. doi: 10.3290/j.ohpd.b871059
68. Polizzi E, Tetè G, Targa C, Salviato B, Ferrini F, Gastaldi G. Evaluation of the Effectiveness of the Use of the Diode Laser in the Reduction of the Volume of the Edematous Gingival Tissue after Causal Therapy. *Int J Environ Res Public Health*. 2020;17(17):6192. doi: 10.3390/ijerph17176192.

69. Athira KV, Bandopadhyay S, Samudrala PK, Naidu VGM, Lahkar M, Chakravarty S. An Overview of the Heterogeneity of Major Depressive Disorder: Current Knowledge and Future Prospective. *Current Neuropharmacology*. 2020;18(3):168-187. doi:10.2174/1570159X17666191001142934