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# Mind Meets Mouth: Probing the Fascinating Interplay of Bipolar Disorder and Periodontal Health

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## Abstract

**Introduction:** Periodontal medicine is a burgeoning field that highlights the intricate relationship between periodontal disease (PD) and systemic health. Although PD has been linked to various systemic conditions, little attention has been given to its potential association with bipolar disorder (BPD). This review investigates the emerging connection between PD and BPD, shedding light on shared risk factors and recent research findings.

**Methods:** PD is a chronic immuno-inflammatory condition affecting tooth-supporting structures, primarily triggered by anaerobic Gram-negative bacteria and resulting in inflammatory responses. BPD, a manic-depressive disorder, is associated with cognitive impairments and heightened suicidality risk. Recent studies suggest that BPD may involve chronic inflammation, oxidative stress, and immune responses. Several cohort studies in Taiwan have identified a significant link between PD and BPD.

**Results**: People with BPD exhibit poorer oral health, reluctance to seek dental care, and higher prevalence of PD due to hygiene neglect and medication-induced dry mouth. Microbial pathogens from PD can breach systemic barriers, potentially leading to neuro-inflammation. Inflammatory mediators in systemic

circulation can activate microglial cells in the central nervous system, contributing to neurodegeneration.

**Conclusion:** While the exact etiology of BPD remains uncertain, mounting evidence suggests a connection between infection and immune-inflammatory processes. Confirmation of this link could open opportunities for early intervention and prevention, addressing a critical gap in the management of cognitive disorders like BPD. Establishing this association may lead to novel strategies for reducing BPD risk by addressing PD as a potential contributing factor.

**Keywords:** Periodontal Disease, Bipolar Disorder, Systemic Inflammation, Oral Health, Neuro-inflammation

## Introduction

The term "periodontal medicine" was first introduced by Steven Offenbacher and encompasses a rapidly growing area of study in Periodontology. It focuses on the substantial body of new evidence that establishes a robust association between the health or disease of the periodontal tissues and systemic health. Over many years, research has established a link between periodontal disease and several systemic conditions such as cardiovascular disease [1], diabetes [2], adverse pregnancy outcome [3] and other disorders (Figure 1).

There is huge list of 57 distinct systemic conditions which are listed as potentially associated to periodontitis till date. [4] Out of all these conditions only two diseases are currently mapped from central nervous system, Dementia and Alzheimer's disease. Bipolar disorder (BPD) is one potential systemic condition which is in primitive stage of assessing the potential association with Periodontal Disease (PD).BPD and PD may seem worlds apart – one affecting the oral cavity, and the other, the complex realm of mental health. Yet, recent research has unveiled an intriguing connection between these seemingly unrelated conditions. This review embarks on a journey to unravel the intricate interplay between PD and BPD, shedding light on shared risk factors that bridge the gap between oral health and mental well-being and briefly review the contemporary association between these two conditions.

## Periodontal Disease

PD is a chronic immuno-inflammatory condition that affects the supporting structures surrounding the teeth. This condition arises due to the presence of anaerobic Gram-negative microorganisms found in the bacterial plaque that attaches to the teeth.The presence of anaerobic Gram-negative bacteria initiates a localized inflammatory response that persists and progresses to the deterioration of alveolar bone along with loss of attachment. Certain microbial components particularly lipopolysaccharide (LPS), leads to activation of macrophages, prompting the secretion of various pro-inflammatory cytokines. These include interleukin-1 (IL-1),tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2), and various other enzymes. Bacterial toxins leads to stimulation of T lymphocytes to generate IL-1 and lymphotoxin (LT), which shares similarities with TNF-α. These cytokines exhibit robust pro-inflammatory and catabolic properties, playing significant roles primarily periodontal destruction fostering the activity of collagen-degrading enzymes, such as metalloproteinases (MMPs). [5]

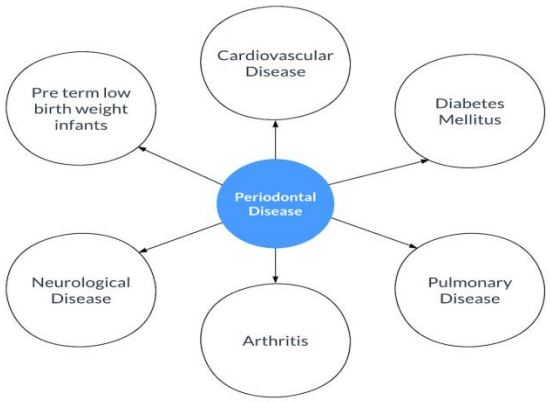


Figure 1: Systemic outcomes of Periodontal Disease,

**Bipolar Disorder**

BPD is a manic-depressive condition that is associated with significant functional and cognitive impairments [6,7 ] as well as an elevated risk of suicidality. [8] More than 1% of the world's population suffers from BPD [9], which is chronic and recurrent in nature and ranked as 17$^{th}$on global illness burden. [10] Although the exact etiology of BPD is not well understood till date, it may arise from a combination of factors which include genetic, environmental, psychological, and potential neurological injuries. [11,12,13] There is growing evidence to understand the neurobiology which encompass both innate and adaptive immune responses affecting central and peripheral nervous system.[14]Emerging evidence suggested that BPD might be linked to chronic inflammation, increased oxidative stress, and immune responses in the brain. [15,16] Meta-analysis by Muneer *et al* [17] confirmed the increase of pro-inflammatory bio markers in BPD suggesting that chronic inflammation is one of the significant factor in etiopathogenesis of BPD. Based on the limited evidence available, it is possible that BPD and PD have shared risk factors.

Huang et al in a nationwide cohort study conducted in Taiwan suggested a significant association between chronic periodontitis (CP) and an elevated risk of subsequent BPD, highlighting a potential link between inflammatory oral disease and psychiatric mood disturbances.[18]

Chang *et al* [19] in a nationwide cohort study found that periodontitis is associated with an increased risk of subsequent BPD, with higher incidence rates observed among patients with CP, suggesting a potential link between oral health and the development of BPD.

Wu *et al* [20] analysed Taiwan National Health Insurance Research Database which revealed that adolescents with BPD exhibit a higher risk of developing PD, emphasizing the importance of preventive oral health measures, especially for those on long-term mood stabilizers.

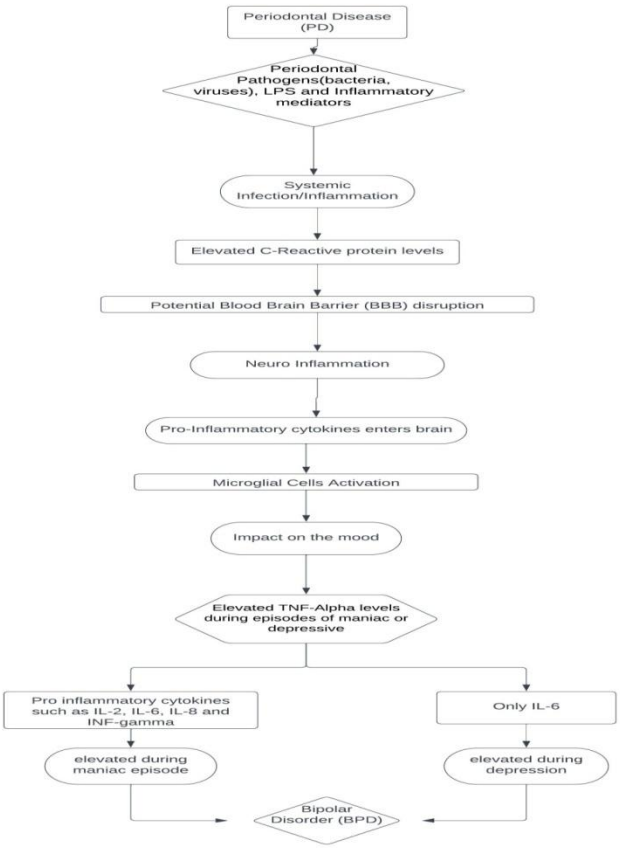


Figure 2: Possible pathway between periodontal disease and Bipolar Disorder (BPD)

**Effects of BPD on Oral health**

Various studies have reported a higher prevalence of poor oral health and periodontal disease in subjects with BPD. [21,22,23] Due to the stigma associated with mental illness, people with BPD may be reluctant to seek oral health care, which increases their risk of developing dental caries and PD. It is established that patients feel less motivated to practice oral hygiene measures during depressive episodes. [24] Conversely, during manic phases, it is presumed that individuals might intensify their oral hygiene practices, potentially resulting in abrasions on enamel and gingival recession in addition to upswing in parafunctional habits leading to attrition as well.[25] Medications used to treat the symptoms of BPD may cause xerostomia, affecting overall oral health. Because of poor oral hygiene and drug-induced xerostomia, the prevalence of PD is higher in patients with BPD often greater. Additionally, people with BPD have been linked to a higher risk of Sjogren's Syndrome development.[26]

Cunha *et al*[27] evaluated the periodontal status in epidemiological and microbiological aspects for individuals with BPD and conducted a multivariate logistic regression analysis which revealed the probability of an individual with BPD having PD was higher in the depression phase than in the manic phase. Hence the authors concluded that individuals with BPD presented a high prevalence of PD.

**Periodontal Pathogens in BPD**

The homeostasis of oral cavity effectively prevents the entry of microorganisms into bloodstream by various barriers, including physical, chemical, and immunological defences. However, when these defences are compromised PD, trauma, or weakened immune responses, microorganismscan easily breach these barriers and can lead to acute or chronic infections. Certain pathogens within plaque have shown the ability to invade intact the pocket epithelium which is characterized by their substantial surface area and potential ulcerations in the lining, providing convenient pathways for pathogens entry into systemic circulation.[28] In advanced stages, PD may lead to systemic inflammation, as evidenced by elevated levels of C-reactive protein in the blood of periodontitis patients compared to controls. [29-31]

Cunha et al [27] showed that patients with BPD exhibited significantly higher amounts of periodontal pathogens A. actinomycetemcomitans and P. gingival is. As a result of periodontal infection, an inflammatory reaction occurs both locally and throughout the body. Inflammatory agents that circulate in the bloodstream might impact the brain through various pathways with humoral and neural pathways being particularly significant.[32] The humoral pathway primarily revolves around the blood-brain barrier (BBB), which governs the movement of substances from the blood into the brain. Periodontal pathogens and virulent products could potentially disrupt the BBB, allowing pro-inflammatory cytokines to enter brain and activate microglia and the immune cells, resulting in neuro-inflammation.[33]

**Systemic inflammation and BPD**

The primary innate immune-defence cells in the central nervous system (CNS) are resident microglial cells.[34] Inflammatory mediators are produced as a result of systemic inflammation as a result of infection which can activate the ‘primed’ microglial cells. These mediators do not necessarily activate all microglial cells. [35,36] The cascade of neurodegeneration that results in a variety of neurodegenerative illnesses is started by the activation of these microglial cells. The microglial cells

are quiescent and ramified in the resting stage.Upon activation, they undergo morphological change towards an amoeboid form.[37] Although microglial cells can be activated by pro-inflammatory stimuli, a pro-inflammatory response is not always the result of this activation. T-helper cells 1 (Th1) in particular are recognized as mediating cellular immune responses and produce cytokines such IL-1, IL-2, IL-6, interferon-gamma, and TNF-alpha. In individuals with BPD experiencing maniac or depressive episodes, elevated TNF-alpha levels have been noted.[38] Pro-inflammatory cytokines such as IL-2, IL-6, IL-8, and INF-gamma were shown to be increased during maniac episode, but only IL-6 was specifically elevated only during depression. Furthermore, an altered ratio of the anti-inflammatory IL-10 to the pro-inflammatory IL-6 was a characteristic feature of BPD.[39] Evidence suggests that successful use of mood stabilizers that results in a euthymic state may be able to reduce inflammation and restore normal levels of inflammatory mediators in both CNS & PNS.[40] (Figure 2)

**Conclusion**

Although the exact mechanism of etiopathogenesis of BPD remains uncertain, substantial evidence points towards the significance of infection and immune inflammatory processes being involved. To elucidate a causative association, investigations employing population-based case-control or cohort designs are imperative. If this link were to be confirmed as valid, it could present a valuable opportunity to identify a factor that can be altered at an early stage, potentially leading to the prevention of BPD later in life. This would be particularly significant in today's era, where there is a shortage of preventive measures for cognitive disorders like BPD. While a cure for BPD is still elusive, establishing a potential connection like this in the future could pave the way for prevention strategies by addressing one of its potential contributing factors, such as PD.

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