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Association between periodontal diseases and bipolar disorder: implications for therapeutic interventions: A narrative review

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Abstract

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Chronic low-grade inflammation plays a role in the pathophysiology of bipolar disorder. Recent studies have shown that periodontitis can affect the central nervous system by activating inflammatory mediators in the brain. However, only a few studies have examined the association between periodontitis and bipolar disorder. Here, we aimed to review the current evidence on the association between periodontal diseases and bipolar disorder, its potential mechanisms, and future research directions. Studies so far suggested that periodontal diseases were more common in patients with bipolar disorder than in the general population. Patients with bipolar disorder generally have poor oral hygiene owing to poor self-care, smoking, alcohol abuse, and the effects of psychotropic medications. Proposed mechanisms underlying this association include the effects of inflammatory mediators, direct invasion of oral microbiota, modulation of the neurotransmitter system, and impact on the vagus nerve and hypothalamus-pituitary-adrenal axis. Additional clinical studies examining the prevalence of periodontal diseases and their association with the clinical features of bipolar disorder are necessary. Clinical studies targeting the treatment of periodontal diseases for primary or secondary prevention of bipolar disorder are warranted.

Keywords: [Bipolar disorder](#); [Neuroinflammation](#); [Periodontitis](#); [Primary prevention](#)

INTRODUCTION

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Bipolar disorder (BD) is characterized by alternating depressive episodes and (hypo-) manic episodes throughout an individual's lifetime. In most cases, BD requires lifetime treatment once diagnosed, owing to the risk of recurrence. Even with the best treatment, many patients experience recurrence. A better understanding of factors implicated in the development or recurrence of mood episodes could help identify new treatment targets. Additionally, patients with BD are known to have a shorter life expectancy than the general population, dying 10 to 15 years earlier than the general population. The major reason for this shorter life expectancy is not suicide but other medical diseases, including cardiovascular disease. Yet, the exact pathophysiological mechanisms and the reasons for the high prevalence of comorbidities in patients with BD are not yet fully elucidated.

Chronic and unresolved inflammation is a potential core pathophysiological mechanism that explains the complex clinical picture of BD involving a high-risk of recurrence and medical burden [1]. Epidemiological studies have reported increased rates of chronic inflammatory comorbidities in patients with BD [2,3]. Patients with BD show increased levels of proinflammatory markers, including cytokines and C-reactive protein (CRP) [4] associated with more severe symptoms [5] and poorer treatment responses [6].

Lithium, one of the oldest and most effective treatments for BD, exerts potent anti-inflammatory effects [7]. For these reasons, clinical trials have been conducted to repurpose anti-inflammatory drugs for BD treatment [8].

The inflammatory basis of BD pathology is not well understood. Genetic factors cannot fully explain the underlying cause. Diverse lifestyle factors, including stressors, trauma, dietary habits, lack of exercise, obesity, and sleep, have been suggested as potential contributors [9].

Oral diseases are highly prevalent but easily neglected physical health conditions in patients with BD [10]. A recent study has shown that periodontitis could be a major source of chronic inflammation associated with cardiovascular and neurodegenerative diseases [11,12]. Considering that both cardiovascular diseases and cognitive dysfunction are disproportionately prevalent in BD, periodontal diseases may be relevant to the pathophysiology of BD. However, very few studies have explored the association between BD and periodontal diseases. This narrative review aimed to examine the inflammatory association between periodontal diseases and BD.

WHAT IS PERIODONTITIS?

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The oral cavity is an ecologically complex microenvironment in the human body. The teeth are the only functional hard tissues extending from the interior to the exterior of the human body, crossing a series of other hard (i.e., bone) and soft (i.e., connective tissue and epithelial) tissues, being surrounded by a resilient biofilm harboring a diverse collection of bacteria. Typically, two common diseases affect the oral tissues and the health of the supporting structures of teeth. Periodontal diseases encompass gingivitis and periodontitis, depending on the severity of inflammatory process in periodontal tissues. Gingivitis is the chronic inflammation limited to the soft tissues, epithelium, and connective tissue, whereas, in periodontitis, the chronic inflammatory processes extend to the supporting tissues, including the alveolar bone [13].

Periodontal diseases are relatively common conditions [14] in both advanced and developing nations, impacting approximately 20% to 50% of people worldwide [12]. Prevalence varies based on age and regions examined, but it is generally more common in older populations. Factors contributing to periodontal diseases include oral hygiene, smoking, stress, diabetes, and compromised immune functions [13].

Periodontitis is classified based on severity. The World Health Organization classifies periodontal disease based on the community periodontal index (CPI) scores. The CPI score ranges from 0 to 4, where a score of 0 indicates healthy periodontal conditions or no periodontal disease, 1 indicates gingival bleeding, 2 indicates calculus and bleeding, 3 indicates shallow periodontal pockets (4 to 5 mm), and 4 indicates deep periodontal pockets (≥ 6 mm) [15]. The most severe form (CPI score 3 or 4) affects 11.2% of the global population, ranking periodontitis as the sixth most prevalent human disease [16].

PERIODONTITIS AND CARDIOVASCULAR DISORDERS

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The association between periodontitis and cardiovascular disorders has been extensively studied [17]. Epidemiological studies demonstrate that periodontitis is associated with increased coronary heart disease [18] and subclinical cardiovascular disease [19]. Although prospective intervention studies are lacking, observational studies have supported the notion that treating periodontitis or improving oral health decreases the risk of acute cardiovascular disease. A recent expert consensus suggested active management of cardiovascular risk factors in patients with periodontitis [17].

PERIODONTITIS AND DEMENTIA

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Among the diseases of the central nervous system (CNS), a meta-analysis supported the association of periodontitis with an increased risk of dementia [11]. Poor periodontal health (reflected by periodontitis, tooth loss, deep periodontal pockets, or alveolar bone loss) is associated with both cognitive decline (odds ratio, 1.23; 95% confidence interval [CI], 1.05 to 1.44) and dementia (hazards ratio, 1.21; 95% CI, 1.07 to 1.38).

However, the overall evidence remains relatively weak [20]. Most studies are based on short-term evaluations. As mentioned earlier, old age is a risk factor for periodontitis, which may introduce unresolved confounding factors. In addition, analysis of dementia studies with ≥ 10 years of follow-up has shown an overall weakening effect of poor periodontal health on dementia, suggesting the possibility of reverse causality.

POTENTIAL MECHANISMS

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Oral microbiota can interact with the CNS through several mechanisms [21]. First, increased levels of inflammatory biomarkers due to oral inflammation can eventually lead to systemic inflammatory sequelae [22]. Elevated levels of CRP, proinflammatory cytokine, and oxidative stress in the blood can subsequently impact neuroinflammation. Second, pathogens associated with periodontitis can directly invade the CNS. Evidence suggests that oral bacterial species can enter the blood circulation and cause bacteremia. In support of this, the presence of periodontitis pathogens has been detected within the brain tissue of individuals with Alzheimer's dementia in postmortem studies [23], and anti-pathogen antibody of periodontitis-causing bacteria has been found in the cerebrospinal fluid of individuals with probable Alzheimer's disease [24]. Third, oral microbiota can impact neurotransmitter metabolism, affecting critical brain networks regulating mood and behavior [25]. Fourth, a recent study suggested that the vagus nerve can serve as a gateway for microbial? Interactions with the CNS [26]. Finally, the oral microbiome can interact with the host's hypothalamic pituitary adrenal axis, resulting in changes in the CNS.

PERIODONTITIS AND BIPOLAR DISORDER

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Few studies have examined the association between periodontitis and BD. No prior research has examined the oral health conditions in patients with BD [10]. Two cross-sectional studies reported a higher rate of periodontitis among patients with BD than in the general population (58.5% vs. 39.7%; 47.1% vs. 16.6%) [27,28]. However, these studies generally included small sample sizes ($n = 352$ and $n = 429$) [29]. One of these studies used nationally representative data. Wu et al. [30] investigated the prevalence of periodontitis in adolescents with BD using the Taiwan National Health Insurance Research Database. They reported that adolescents with BD

had a higher risk of periodontitis than those without BD. Furthermore, long-term use of mood stabilizers was associated with a higher risk of periodontitis in those with BD.

A higher rate of periodontitis has been reported in patients with severe mental illness compared to the general population. A UK Biobank study reported that periodontal disease is more frequent in patients with psychosis compared to the general population (21.3% vs. 14.8%) [31]. Brief self-report questionnaires were used to evaluate the presence of periodontitis. A study using medical records from the Veteran Affairs Health System also reported a higher rate of poor oral health problems in patients with severe mental illness [32].

Poor self-care during mood episodes, high smoking rates, frequent alcohol abuse rates, psychotropic-induced side effects (e.g., xerostomia, dysgeusia, and stomatitis), and non-compliance with dental clinic visits have been suggested as potential causes for poor oral health and the development of periodontitis in patients with BD [33,34]. However, as previous studies on cardiovascular diseases and dementia suggested, the opposite causal relationship also should be considered. Heightened inflammation associated with periodontitis could increase the risk of BD. Another Taiwan National Health Insurance Research Database study examined the association between periodontitis and newly onset BD [35]. They observed that the incidence rate of BD was higher in the periodontitis group than in the non-periodontitis group (2.74 vs. 1.46 per 1,000 person-year), with an adjusted hazard ratio of 1.82 (95% CI, 1.59 to 2.08) after adjusting for sex, age, and comorbidities.

A study compared the oral microbiome of patients with BD to that of the general population [27]. The total bacterial load was more significant in patients with BD, and the numbers of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* were significantly higher in patients with BD.

FUTURE STUDY DIRECTIONS

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As stated above, periodontitis might be associated with BD's development, illness course, and treatment response. However, evidence supporting this association remains scarce. To confirm this association, we need studies that start with a comprehensive assessment of the prevalence of periodontitis among patients with BD and an exploration of the causal relationship between periodontitis and new-onset BD using nationally representative data, such as health examination data or claims data provided by the South Korean National Health Insurance System. Electronic health record data can also be used to determine the incidence of periodontitis in individuals with BD.

Data directly collected from clinical populations is also necessary. A simple screening questionnaire can be administered to patients with BD. The Oral Health Impact Profile 14 (OHIP-14) questionnaire [36] is a questionnaire widely used to evaluate oral health encompassing seven dimensions (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap) based on the theoretical model proposed by Locker [37]. The OHIP-14 scores range from 0 to 56 and are calculated by summing the ordinal values for the 14 items, with higher scores indicating worse oral health. Even without a standardized questionnaire, clinicians can ask their patients about their oral health, including inquiries about the presence of teeth, toothache, gum bleeding, mouth odor, teeth sensitivity, patients' brushing habits, and reports of gum disease or oral cancer. Basic information on the oral health of patients with BD will provide psychiatrists with a comprehensive overview of the frequency of periodontitis in these patients and its association with clinical features.

Indeed, studies including direct periodontal clinical examinations in patients with BD are also necessary. Through oral examination, bleeding on probing, probing depth, and clinical attachment levels of all existing teeth can be assessed. In addition, the association between the severity of periodontitis and the severity or symptom characteristics of BD should be examined. Acquiring information on oral microbiota and its association with symptom severity or characteristics of BD is essential. Furthermore, subgingival samples can be collected to examine the composition of oral microbiota. Conducting studies across diverse populations is imperative since microbial composition can vary based on cultural and ancestral backgrounds [21].

Studies exploring the association between periodontitis and BD are promising because periodontitis presents a potentially modifiable risk factor or course-modifying factor for BD. No study has focused on the treatment interventions for periodontitis in patients with BD. Observational studies have suggested that oral health interventions, from simple self-administered oral hygiene habit education to actual periodontal treatment, reduce cardiovascular disease incidence [17]. Likewise, dental hygiene care as a primary prevention strategy for BD in high-risk populations can be attempted. In addition, secondary and tertiary prevention can be attempted in patients with BD, considering that symptom severity and recurrence are associated with inflammatory levels.

CONCLUSION

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BD is a debilitating mental disorder, often accompanied by diverse physical conditions and decreased life expectancy. Inflammation and its potential effects on brain function are one possible pathophysiological mechanism in BD, which should be considered as a potential new treatment target. However, a better understanding of “where inflammation comes” from is needed for this treatment target to yield the most successful interventions. Periodontitis is a potentially significant contributor. Although the existing body of research is limited, previous studies have demonstrated the potential of periodontitis as a link for understanding the association between inflammation and BD. Further studies are warranted to explore the association between periodontitis and BD in diverse cultural and ethnic populations.

CONFLICTS OF INTEREST

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No potential conflict of interest relevant to this article was reported.

Notes

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AUTHOR CONTRIBUTIONS

Conception or design: JHB, AAN.

Acquisition, analysis, or interpretation of data: AP, AK, AAN.

Drafting the work or revising: JHB, SJJ, AP, AK, AAN.

Final approval of the manuscript: JHB, SJJ, AP, AK, AAN.

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