Observational Study

Association between periodontitis and bipolar disorder

A nationwide cohort study

Kuang-Hsi Chang, PhD\textsuperscript{a,b,c}, Yi-Chao Hsu, PhD\textsuperscript{d}, Ing-Ming Chiu, PhD\textsuperscript{e}, Lih-Chyang Chen, PhD\textsuperscript{f}, Chih-Chao Hsu, MD\textsuperscript{g}, Chang-Yin Lee, PhD\textsuperscript{h,i,j}, Hueng-Chuen Fan, PhD\textsuperscript{k,l}, Hsuan-Ju Chen, MSc\textsuperscript{m}, Ruey-Hwang Chou, PhD\textsuperscript{n.o.p,q,r,s},

Abstract

Whether periodontitis is a risk factor for developing bipolar disorders (BD) has not been investigated. We aimed to determine whether periodontitis is associated with the subsequent development of BD and examine the risk factors for BD among patients with periodontitis.

Using ambulatory and inpatient claims data from the National Health Insurance Research Database (NHIRD), we identified 12,337 patients who were aged at least 20 years and newly diagnosed with periodontitis between 2000 and 2004. The date of the first claim with a periodontitis diagnosis was set as the index date. For each patient with periodontitis, 4 subjects without a history of periodontitis were randomly selected from the NHIRD and frequency-matched with the patients with periodontitis according to sex, age (in 5-year bands), and index year.

The periodontitis group had a mean age of 44.0 ± 13.7 years and slight predominance of men (51.3%). Compared with the subjects without periodontitis, the patients with periodontitis had higher prevalence of diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, head injury, major depressive disorder, chronic obstructive pulmonary disease (COPD), and asthma (\(P < .001\)). The incidence rate of BD was higher in the periodontitis group than in the non-periodontitis group (2.74 vs 1.46 per 1000 person-year), with an adjusted hazard ratio of 1.82 (95% confidence interval=1.59–2.08) after adjustment for sex, age, and comorbidities.

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K-H C and Y-C H have contributed equally to this work.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. The dataset is owned by the Taiwan National Health Research Institutes (NHRI). Requests for the data set may be sent an e-mail to the NHRI at nhird@nhri.org.tw or call at +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).

The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

* Department of Medical Research, \textsuperscript{a} Graduate Institute of Biomedical Sciences, China Medical University, \textsuperscript{b} General Education Center, \textsuperscript{c} Institute of Biomedical Sciences, \textsuperscript{d} Institute of Cellular and System Medicine, National Health Research Institutes, \textsuperscript{e} Department of Medicine, Mackay Medical College, New Taipei City, \textsuperscript{f} Division of Psychiatry, Taitung Branch, Taipei Veterans General Hospital, Taitung, \textsuperscript{g} College of Medicine, The School of Chinese Medicine for Post Baccalaureate, I-Shou University (Yancho Campus), \textsuperscript{h} Department of Chinese Medicine, E-DA Hospital, \textsuperscript{i} Department of Chinese Medicine, E-DA Cancer Hospital, Kaohsiung, \textsuperscript{j} Department of Pediatrics, Tungs’ Taichung MetroHarbor Hospital, \textsuperscript{k} Department of Rehabilitation, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, \textsuperscript{l} Management Office for Health Data, \textsuperscript{m} Center for Molecular Medicine, China Medical University Hospital, \textsuperscript{n} Department of Biotechnology, Asia University, Taichung, Taiwan.

Correspondence: Ruey-Hwang Chou, Graduate Institute of Biomedical Sciences, China Medical University, No.91, Hsueh-Shin Road, North District, Taichung 404, Taiwan (e-mail: rchou@mail.cmu.edu.tw).

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1. Introduction

Periodontitis is initiated by bacterial plaque biofilm and can be caused by gingivitis affecting soft tissues near the teeth, resulting in the destruction of the tissue supporting the teeth. Periodontal tissue respond to bacterial invasion by mobilizing defense cells and releasing inflammatory cytokines, such as interleukins (ILs), tumor necrosis factor alpha (TNF-α) and prostaglandin E2 (PGE2), which may cause tissue destruction by stimulating the production of enzymes such as matrix metalloproteinase. Evidence is mounting for possible associations between periodontitis and other diseases such as depression, diabetes mellitus, atherosclerotic cardiovascular disease, and rheumatoid arthritis.

Bipolar disorder (BD) is a disabling, recurrent mental illness that varies widely in severity. The onset of BD is typically observed in late childhood or early adolescence. Patients with BD have higher rates of comorbidities of psychiatric disorders and other medical conditions, which might entail an increased medical burden and multiple physical abnormalities. Early detection and treatment of BD can improve patient outcomes. One study suggested that patients with BD are at high risk of dental diseases. When patients are in depressive episodes, they may pay less attention to oral hygiene, leading to an increase in dental diseases. When patients are in depressive episodes, they may pay less attention to oral hygiene, leading to an increase in dental diseases.

Although the association between periodontitis and psychiatric conditions, such as major depressive disorders and cognitive decline, remains controversial, periodontitis has been suggested as a risk factor for dementia. Whether periodontitis is a risk factor for developing subsequent BD has not been investigated. In this study, we hypothesized that periodontitis increases the risk of BD. To test our hypothesis, we conducted a nationwide population-based study to investigate the incidence and risks of BD among patients with or without periodontitis.

2. Patients and methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was implemented in 1995. At the end of 2014, the program was providing health care to approximately 99% of the Taiwan population (23.75 million people). The NHI is a mandatory health insurance program that offers comprehensive medical care coverage to all residents of Taiwan. The National Health Insurance Research Database (NHIRD) is managed and maintained by the National Health Research Institutes (NHRI) according to the directives of the National Health Insurance Administration. Our study used the Longitudinal Health Insurance Database (LHID2000), which contains the data of 1 million enrollees sampled from the medical claim records of the NHI from 1996 to 2011. The LHID2000 contains comprehensive outpatient and inpatient data, including demographic, clinical visit, and prescription information, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To ensure privacy protection, the NHRI encrypts and converts the identification numbers of all NHIRD records before releasing them for research. Our study was exempted from review by the Institutional Research Ethics Committee of China Medical University (CMU-REC-101-012), Taiwan.

2.2. Study population

Using the ambulatory and inpatient claims data sets, the inclusion criteria for this study of patients with periodontitis included being 20 years old or older and newly diagnosed with periodontitis (ICD-9-CM 523.4x and 523.5x) between 2000 and 2004. The date of the first claim with a periodontitis diagnosis was considered as the index date. For each patient with periodontitis, subjects with no history of periodontitis (ICD-9-CM 523.xx) were randomly selected from the NHIRD and frequency-matched according to sex, age (in 5-year bands), and index year. The definition of BD patients was based on the following criteria: patients with a diagnosis of BD (ICD-9-CM code 296.xx) at least 3 times before the index date. However, patients who developed BD within 1 month after the index date were excluded. Finally, the periodontitis and non-periodontitis groups comprised of 12,337 and 49,348 patients, respectively. The ICD-9 code 523.4 includes the symptoms of chronic periodontitis, including chronic pericoronitis, chronic periodontitis (no otherwise specific, complex, and simplex), but excludes chronic apical periodontitis (ICD 9 code: 522.6). ICD-9 code 523.5 refers to the type of periodontitis with diffuse atrophy of the alveolar bone. Demographic data included sex and age (20–34 years, 35–49 years, 50–64 years, and ≥65 years). We also recorded claims data on comorbidities before the index date on DM (ICD-9-CM 250.xx), hyperlipidemia (ICD-9-CM 272.xx), hypertension (ICD-9-CM 401.xx–405.xx), ischemic heart disease (IHD, ICD-9-CM 410.xx–414.xx), stroke (ICD-9-CM 430.xx–438.xx), head injury (ICD-9-CM 850.xx–854.xx and 959.01), alcohol abuse and dependence (ICD-9-CM 303.xx, 305.0x, and V11.3), major depressive disorder (ICD-9-CM 296.2x, 296.3x, 311.xx, 316.xx, 318.81-318.89).
300.4x, and 309.0x). Smoking status and alcohol consumption were not available in NHIRD. Thus, we performed the multivariate analysis by adjusting for tobacco related diseases (including tobacco dependence [ICD-9-CM codes 305.1], chronic obstructive pulmonary disease [ICD-9-CM codes 490–492, 494, and 496], and asthma [ICD-9-CM code 493]).

The primary outcome was a diagnosis of BD (ICD-9-CM code 296.xx), which was determined by linking the NHIRD ambulatory and inpatient data. All study participants were observed from the index date to BD diagnosis, withdrawal from the NHI program, or the end of 2011.

2.3. Statistical analysis

Summary statistics are expressed as frequencies and percentages for categorical data and means and standard deviations (SDs) for continuous variables. The Pearson chi-square test and Student t test were used to compare categorical and continuous variables, respectively, between the patients with and without periodontitis. The sex, age-, and comorbidity-specific incidence rates of BD were measured for both groups. The Kaplan–Meier method was used to depict the cumulative incidence of BD for the groups. The log-rank test was used to test the difference between the curves. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for determining whether periodontitis is a risk factor for the development of BD, and the models were adjusted for sex, age, DM, hyperlipidemia, hypertension, IHD, stroke, head injury, alcohol abuse/dependence, and major depressive disorder. We also performed sex-, age-, and comorbidity-stratified analysis to investigate the association between periodontitis and the risk of BD. All the data processing and statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). A 2-sided P value of <.05 was considered statistically significant.

3. Results

We identified 12,337 patients with periodontitis from 2000 to 2004 as the periodontitis group and frequency-matched them with 49,348 subjects without periodontitis according to sex, age, and year of periodontitis diagnosis. Table 1 contains the demographics and comorbidities of the patients with and without periodontitis. The mean age of the periodontitis group was 44.0 years (SD = 13.7 years), with a slight predominance of men (51.3%). The patients with periodontitis had higher prevalence of DM, hyperlipidemia, hypertension, IHD, stroke, head injury, and major depressive disorder, chronic obstructive pulmonary disease (COPD), and asthma than the subjects without periodontitis (all P < .001).

Figure 1 showed the results of the log-rank test and the cumulative incidences of BD. The Kaplan–Meier analysis was used to determine the risk of BD during follow-up in both groups. The cumulative incidence of BD was significantly higher in the periodontitis group than in the non-periodontitis group (P < .001).

During the average follow-up of 8.79 years, 339 (2.76%) patients in the periodontitis group and 611 (1.46%) patients in the non-periodontitis group developed BD. The incidence rate of BD was higher in the periodontitis group than in the non-periodontitis group (2.76 vs 1.46 per 1000 person-year), with an adjusted HR (aHR) of 1.82 (95% CI = 1.59–2.08) after adjustment for sex, age, and comorbidities (Table 2). In a multivariate Cox regression analysis, men exhibited a lower risk of BD than women did (aHR = 0.59, 95% CI = 0.52–0.68). Compared with the patients without counterpart comorbidities, higher risks of BD were observed in those with comorbidities of hyperlipidemia (aHR = 1.42, 95% CI = 1.16–1.74), hypertension (aHR = 1.34, 95% CI = 1.11–1.62), IHD (aHR = 1.52, 95% CI = 1.22–1.89), head injury (aHR = 1.85, 95% CI = 1.23–2.79), alcohol abuse or dependence (aHR = 9.43, 95% CI = 4.66–19.1), major depressive disorder (aHR = 7.42, 95% CI = 5.86–9.41), and COPD (aHR = 1.36, 95% CI = 1.04–1.77).

Stratified by sex, the higher risks of BD in patients with periodontitis were exhibited by both women (aHR = 1.68, 95% CI = 1.42–2.00) and men (aHR = 1.87, 95% CI = 1.51–2.32) compared with the subjects without periodontitis. Stratified by age group, the patients with periodontitis had a significantly
higher risk of BD compared with the subjects without periodontitis in all age categories. The aHRs of BD were 1.76 (95% CI = 1.26–2.45) for those aged 20 to 29 years, 1.80 (95% CI = 1.32–2.47) for those aged 30 to 39 years, 1.74 (95% CI = 1.33–2.27) for those aged 40 to 49 years, and 1.68 (95% CI = 1.35–2.08) for those aged 50 years or older. Regardless of the subjects’ comorbidity status, patients with periodontitis had a higher risk of BD than subjects without periodontitis (aHR = 1.80, 95% CI = 1.50–2.16 for those without comorbidity and aHR = 1.78, 95% CI = 1.47–2.17 for those with comorbidity) (Table 3).

4. Discussion
Periodontitis is a highly prevalent oral disease initiated by a bacterial plaque biofilm[1] around the teeth resulting in chronic inflammation in adjacent soft tissue. In routine dental procedures, even tooth brushing, these bacteria and their components, such as endotoxin, can be easily disseminated into the systemic circulation through minor or major gingival injuries. Notably, in immunocompromised people or patients with preexisting pathologic oral conditions, bacteremia may lead to the bacterial infection of distant organs, which may elicit immunological
Table 3
Incidence rates and hazard ratios of bipolar disorder according to periodontitis status and stratified by sex, age, and comorbidities.

| Characteristics | No BP no. | PY | IR | Yes BP no. | PY | IR | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-----------------|----------|----|----|------------|----|----|-------------------|----------------------|
| **Sex**         |          |    |    |            |    |    |                   |                      |
| Women           | 385      | 207896 | 1.85 | 203 | 50653 | 3.39 | 1.84 (1.55–2.18) | 1.68 (1.42–2.00) |
| Men             | 226      | 212275 | 1.06 | 136 | 62788 | 2.17 | 2.06 (1.66–2.56) | 1.87 (1.51–2.32) |
| **Age, y**      |          |    |    |            |    |    |                   |                      |
| 20–29           | 96       | 70086 | 1.37 | 56  | 22620 | 2.48 | 1.84 (1.33–2.56) | 1.76 (1.26–2.43) |
| 30–39           | 110      | 89439 | 1.23 | 63  | 26467 | 2.38 | 1.93 (1.41–2.63) | 1.80 (1.32–2.47) |
| 40–49           | 164      | 129226 | 1.27 | 85  | 35562 | 2.39 | 1.89 (1.45–2.46) | 1.74 (1.33–2.27) |
| ≥50             | 261      | 13171 | 1.84 | 135 | 37905 | 3.55 | 1.96 (1.58–2.42) | 1.68 (1.35–2.08) |
| **Comorbid status** |       |    |    |            |    |    |                   |                      |
| No              | 362      | 325020 | 1.11 | 173 | 85537 | 2.02 | 1.81 (1.51–2.17) | 1.80 (1.50–2.16) |
| Yes             | 249      | 94841 | 2.63 | 166 | 37104 | 4.47 | 1.74 (1.43–2.12) | 1.78 (1.47–2.17) |

BP no. = number of patients with BP, CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 = person-years, PY = person-years.

1 Patients with a comorbidity of diabetes mellitus, hyperlipidemia, hyper tension, ischemic heart disease, stroke, heart failure, alcohol abuse or dependence, major depressive disorder, COPD, asthma, and tobacco dependence were enrolled in the comorbidity group.

2 Mutually adjusted for sex, age (continuous), and comorbidity in Cox proportional hazards regression.

responses. Oral bacteria and endotoxins have also been associated with the occurrence of lung infection, sepsis, liver disease, and infective endocarditis,[33] but not with BD.

Our results revealed that the patients with periodontitis were at a significantly increased risk of BD. According to our analysis of the risk factors for BD in patients with periodontitis, we suggested that a possible mechanism is the interaction between chronic inflammation and the hypothalamic–pituitary–adrenal (HPA) axis. The key structures comprising the HPA axis are the paraventricular nucleus (PVN) of the hypothalamus, anterior lobe of the pituitary gland, and adrenal gland.[27,28] In addition, recent studies have demonstrated that chronic inflammation is associated with BD.[29–32] The immune reaction and proinflammatory cytokines, such as ILs and TNF-α, could induce neuroinflammation.[13] Lipopolysaccharide, a membrane component of Gram-negative bacteria, is an endotoxin and has been shown to stimulate microglia to produce numerous proinflammatory cytokines, such as TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6).[34] Likewise, inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-17 have been shown to be increased in patients with chronic periodontitis. Elevated secretion of these cytokines contributes to acute and chronic inflammation and tissue injury, leading to increased risk of systemic diseases such as cardiovascular diseases, DM, cancer, and chronic respiratory diseases.[35–37] Interestingly, the serum levels of anti-inflammatory cytokines, IL-4, and IL-10 were reduced in patients with chronic periodontitis.[37,38] Therefore, periodontitis may result in a local infection and thereafter induce inflammatory cascades, thus increasing the susceptibility to other severe pathological conditions such as cardiovascular disease[35–39] and DM.[41] Notably, it has been shown that proinflammatory cytokines, such as IL-1β, can be detected in PVN. The upregulation of IL-6 and COX-2 has also been detected in the adrenal glands. These findings provide novel insight into the relationship between proinflammatory cytokines within key structures comprising the HPA axis.[27] Furthermore, chronic inflammation may disturb the HPA axis and induce hypercortisolism and neuroinflammation through a proinflammatory cascade.[27,42,43] In addition to inducing neuroinflammation, proinflammatory cytokines could also induce indoleamine 2,3-dioxxygenase, thus reducing the availability of tryptophan and disturbing serotonin synthesis.[14] Immune-inflammatory pathways and cytokine changes in BD have been linked to changes in oxidative stress, nitrosative stress, and tryptophan catabolites.[14] As a result, the risk of BD was increased among patients with periodontitis.

It has been reported that periodontitis is a risk factor of dementia. That is not a concrete causality research, instead that is an association study. Two research designs have been used on the similar topics, namely case-control study[10] and retrospective cohort study.[45] For the case-control study, they enrolled the cases with (experimental group) or without (control group) cognitive impairment or dementia, and analyzed the association with periodontitis to evaluate its risk to dementia.[10] For the retrospective cohort study, they enrolled the patients diagnosed with periodontitis during 2003 to 2004, followed up for overall dementia, Alzheimer disease, and vascular dementia until 2015, and retrospectively analyzed the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of dementia according to chronic periodontitis.[13] The experimental design of our current study was similar to the later one as a retrospective cohort study. Periodontitis represented a source of systemic inflammation,[46] and chronic inflammation is associated with dementia.[9,10,47] as well as BD,[12,32] suggesting that the mechanism of periodontitis increasing the risk to dementia and BD might share similar factors, at least in part, including inflammation.

In addition to inflammation, smoking is also a common risk factor for both periodontitis and BD. A previous study demonstrated that smoking and oral pain are factors related to the prevalence and risk of periodontitis among adults with or without DM.[48] Similarly, smoking is about 2 to 3 times common in adults with BD compared with the general population.[49] The associations may be related to lower levels of serotonin, which contributes to brain serotonergic function[50,51] in smokers. The associations between smoke-related diseases such as COPD, asthma, and tobacco dependence with periodontitis and BD were also evaluated in the current study. The results showed that the patients with periodontitis had higher prevalence of COPD and asthma compared with those without periodontitis (Table 1), and the patients with BD had higher risk of COPD (aHR 1.36, 95%
This population-based study specifically examined periodontitis as a risk factor for BD by using matched cohorts. The major finding of our study is that the incidence of non-periodontitis group was lower than the non-periodontitis group, the prevalence of HT and IHD in the periodontitis group was still higher. This might be due to the shorter follow-up period in the periodontitis group. Both HT and IHD usually occur before the onset of stroke. Because the periodontitis patients had higher risk of comorbidities, the non-periodontitis group was more active. This resulted in higher risk of head injury caused by vehicle accidents. Moreover, the patients with periodontitis might be more likely to stop drinking alcohol which may have contributed to the slightly higher (but not statistically significant) prevalence of alcohol abuse in the non-periodontitis group.

5. Conclusion

We propose that patients with BD exhibit a significantly increased risk of developing BD. Accordingly, we suggest that, following the diagnosis of BD, practitioners could notice the occurrence of the symptoms of BD, and associated prevention. Additional prospective studies investigating the relationship between periodontitis and BD are warranted.

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Author contributions

Collection and assembly of data: Kuang-Hsi Chang, Yi-Chao Hsu, Ing-Ming Chiu, Lih-Chyang Chen, Chih-Chao Hu, Chang-Yin Lee, Hueng-Chuen Fan, Hsuan-Ju Chen, Ruey-Hwang Chou.

Conception/Design: Yi-Chao Hsu, Ruey-Hwang Chou.

Data analysis and interpretation: Kuang-Hsi Chang, Yi-Chao Hsu, Ing-Ming Chiu, Lih-Chyang Chen, Chih-Chao Hu, Chang-Yin Lee, Hueng-Chuen Fan, Hsuan-Ju Chen, Ruey-Hwang Chou.

Final approval of manuscript: Kuang-Hsi Chang, Yi-Chao Hsu, Ing-Ming Chiu, Lih-Chyang Chen, Chih-Chao Hu, Chang-
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