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Correlation between diabetes mellitus and periodontitis in Taiwan: A nationwide cohort study

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ABSTRACT

Aims: The mechanism underlying the association of diabetes mellitus (DM) and periodontitis is not clear. This study aimed to investigate the correlation between DM and periodontitis.

Methods: This study was a retrospective cohort study, which conducted based on the Taiwan National Health Insurance Research Database. The study subjects were 39,384 new-onset DM patients who aged above 20 years old from 2005 to 2012. To avoid selection bias, we applied propensity score matching to obtain patients without DM, as the control group. Cox proportional hazard model was used to analyze the risk of periodontitis in patients with DM.

Results: After controlling for related variables, Patients with DM had a higher risk for periodontitis compared with the patients without DM (adjusted hazard ratios [aHR] = 1.04, 95% confidence interval [CI]: 1.01–1.08). Patients with hypertension (HTN) had no higher risk for periodontitis (aHR = 0.96, 95% CI: 0.92–1.00). Patients with dyslipidemia and rheumatoid arthritis (RA) patients both had a higher risk for periodontitis (aHR = 1.26, 95% CI: 1.19–1.34; aHR = 1.41, 95% CI: 1.19–1.67).

Conclusions: There is a correlation between DM and periodontitis. Patients with DM may have a higher risk of incident periodontitis. Besides, age, HTN, dyslipidemia, and RA are also associated with incident periodontitis.

1. Introduction

There has recently been much emphasis on the two-way relationship between diabetes mellitus (DM) and periodontitis, with more severe periodontal tissue destruction in diabetic patients and poorer glycemic control in diabetic subjects with periodontal disease [1,2]. DM a significant risk factor for periodontitis, periodontal disease has a higher incidence in diabetic patients, and it is more prevalent and severe if compared with the healthy population [1,3]. The risk of

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periodontitis is greater if glycaemic control is poor. DM has been unequivocally confirmed as a major risk factor for periodontitis [4]. Controlling diabetes (i.e. improving glycaemic control) is likely to reduce the risk and severity of periodontitis. People with poorly controlled diabetes (most at risk for the other macrovascular and microvascular complications) are at an increased risk of periodontitis and alveolar bone loss [5].

Periodontitis is a common chronic inflammatory disease characterized by the destruction of the periodontal tissues and resulting in the loss of connective tissue attachment. The risk of periodontitis is increased by approximately threefold in diabetic individuals compared with non-diabetic individuals [6]. Severe periodontitis at baseline was associated with an increased risk of poor glycaemic control (HbA1c > 9.0%) at follow-up (minimum 2 years), suggesting that severe periodontitis was a risk factor for poor glycemic control. This study suggests that physicians treating patients with DM should be alert to the signs of severe periodontitis in managing DM [7]. In fact, aggressive periodontitis is recognized as the sixth complication of diabetes, the other five complications are retinopathy, neuropathy, nephropathy, cardiovascular disease and peripheral vascular disease [8,9]. Resolution of periodontal inflammation can improve metabolic control (with reported HbA1c reductions of approximately 0.4%) [1].

In patients with DM, the risk of periodontitis has a higher incidence compared with a healthy population, which is clinically concern issue. However, relative research is less in Taiwan, especially based on nationwide database. This study aims to investigate the correlation between DM and periodontitis from the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Materials and methods

2.1. Data source

This nationwide retrospective cohort study was based on the data from Longitudinal Health Insurance Database (LHID), which was randomly selected from the NHIRD provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes (Registered number NHIRD-104-312). The LHID comprises the data of detailed clinical records from patient visits, primary and secondary diagnostic codes, and prescription orders for one million randomly selected beneficiaries of the National Health Insurance (NHI) program. The NHI program of Taiwan has been launched since 1995 and >99% of citizens are all enrolled in the program. Therefore, the NHIRD can represent the utilization conditions of medical resources for the 23 million residents and is one of the largest databases universally. This study was exempted from informed consents because the personal identification data were encrypted and transformed in the NHIRD.

2.2. Study subjects

The participants were the new-onset DM patients who aged above 20 years old. The definition of DM was DM diagnosis three times a year, which according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 250 and 251. We excluded patients who had suffered periodontitis before had DM to reduce the study bias. Furthermore, we used the propensity score matching (PSM) to obtain patients without DM in 1:1 matching for each DM patient on the year of enrollment (i.e., 2005, 2006, 2007, until 2012), via gender and age, as the control group. In addition, the patients without DM who we selected for the control group was had no received any DM diagnosis during the study period. The propensity score is the probability that a unit with certain characteristics will be assigned to patients with DM. The scores could be used to reduce or eliminate selection bias in observational studies by the characteristics of patients with and without DM.

2.3. Study designs

This study was conducted using 2004–2013 claim data from LHID. We enrolled patients with and without DM from 2005 to 2012 as the study subject, to ensure that exclusion condition and each patient had least one years of follow-up. Fig. 1 lists flowchart of selection patients for inclusion. We enrolled 39,384 patients with DM and 39,384 patients without DM between 2005 and 2012, respectively. Each patient was follow-up until the date of incident periodontitis, death, or the end of 2013, whichever occurred first. We estimated the risk of periodontitis in patients with DM during the study period. The definition of periodontitis in the study was based on the diagnosis according to the ICD-9-CM codes 523.0x-523.5x.

The study used the Cox proportional hazard model to estimate the hazard ratios with 95% confidence interval (CI) for the association between DM and periodontitis, after controlling for related variables. Control variables were gender, age, monthly insured income, Charlson comorbidity index (CCI) score, and comorbidity diseases. The DM and DM with end-organ damage are both the one of index list in CCI score, so exclude these two conditions scoring when calculated CCI score in the study. The comorbidity disease contained hypertension (HTN) (ICD-9-CM codes 401-405), dyslipidemia (ICD-9-CM code 272), and rheumatoid arthritis (RA) (ICD-9-CM code 714).

All statistical analyses in the study were using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance in this study was defined as $p < 0.05$.

3. Results

3.1. The baseline characteristics of study subjects after propensity score matching

Table 1 indicated the basic characteristics of patients with and without DM after matching. There were total 78,768 participants in the study, after matching. The male were 41,214 (52.32%) and the female were 37,554 (47.68%) in the study. The average age of patients with DM was 58.05 years old and standard deviation (SD) was 13.81 years old; the age of patients without DM was 57.65 ± 15.99 years old. As expected, the characteristics of matching variables were similar, include

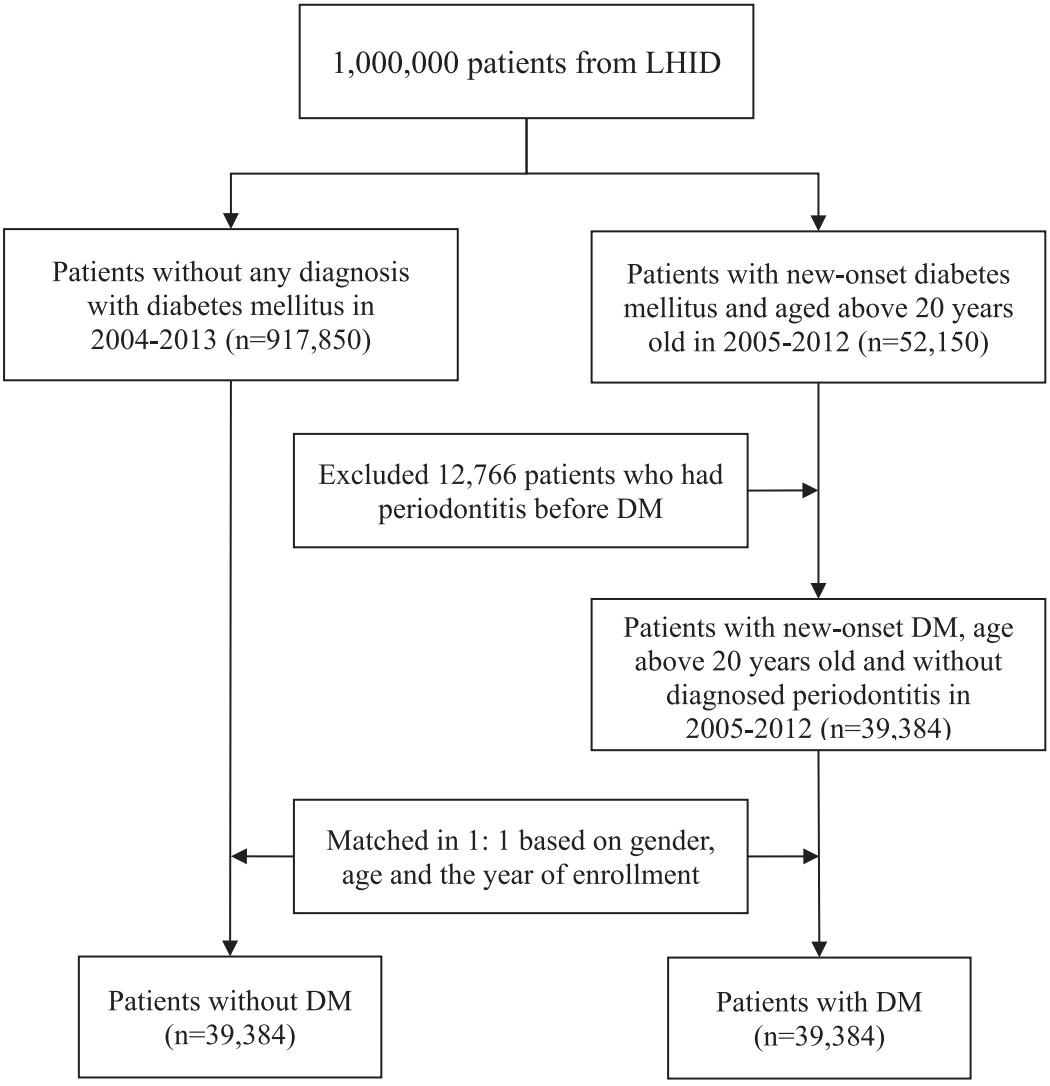

Fig. 1 – Flowchart of the study subject selection process.

gender and age between the patients with DM and without DM ($p = 1.000$), after matching. Among patients with DM, there were 14,776 patients (37.52%) with HTN, 5,825 patients (14.79%) with dyslipidemia and 202 patients (0.51%) with RA. Furthermore, the table showed that the distribution of each comorbidity disease had a statistically significant difference between the patients with and without DM ($p < 0.001$).

3.2. *Characteristics of covariates associated with periodontitis*

The average age of all participants was 57.85 ± 14.94 years old. As the Table 2 showed, among the 78,768 participants, 15,170 patients (19.26%) had occurred periodontitis. The age of patients with periodontitis was 55.03 ± 12.77 years old, and the age of patients without periodontitis was 58.52 ± 15.34 years old. The male patients had a higher percentage on incident periodontitis, compared with female patients (19.54% vs. 18.95%, $p = 0.033$). The distributions of periodontitis had a statistically significant difference between patients with and without DM ($p = 0.033$), although the incidence of periodontitis was similar (18.96% vs. 19.56%). The patients with dyslipidemia had a higher percentage on incident periodontitis, compared with the patients without dyslipidemia (22.13% vs. 18.90%, $p < 0.001$). The patients with RA also had a higher percentage on incident periodontitis (23.85% vs. 19.22, $p < 0.001$, compared without RA). In addition, the other covariates associated with periodontitis had a statistically significant difference, includes age, monthly insured income and CCI ($p < 0.001$).

3.3. *Correlation between DM and periodontitis*

The Table 3 shows the adjusted hazard ratios (aHR) for periodontitis among patients with and without DM. After controlling for other relevant influencing factors, the Table 3 indicated that patients with DM had a higher risk being aHR of 1.04 (95% CI: 1.01–1.08) than patients without DM. Patients who aged 41–54 and 55–64 years old both had a higher risk for periodontitis compared with the 20–40 years old patients (aHR = 1.24, 95% CI = 1.16–1.31; aHR = 1.18, 95% CI = 1.10–1.26). Patients who had more monthly insured income had

Table 1 – The baseline characteristics of study subjects after propensity score matching.

Variables	Total		Patients Without DM		Patients With DM		p-value[1]
	N	%	N	%	N	%	
Total	78,768	100.00	39,384	50.00	39,384	50.00	
Gender[2]							1.000
Female	37,554	47.68	18,777	47.68	18,777	47.68	
Male	41,214	52.32	20,607	52.32	20,607	52.32	
Age (years)[2]	57.85 ± 14.94		57.65 ± 15.99		58.05 ± 13.81		1.000
20–40	9,018	11.45	3,959	10.05	3,959	10.05	
41–54	25,504	32.38	12,331	31.31	12,331	31.31	
55–64	18,926	24.03	10,434	26.49	10,434	26.49	
≧65	25,320	32.15	12,660	32.15	12,660	32.15	
Monthly insured income (NTD.)							<0.001
≦17,280	14,101	17.90	7,053	17.91	7,048	17.90	
Dependents[3]	19,738	25.06	9,438	23.96	10,300	26.15	
17,281–22,800	24,454	31.05	12,188	30.95	12,266	31.14	
22,801–28,800	4,762	6.05	2,422	6.15	2,340	5.94	
28,801–36,300	4,659	5.91	2,418	6.14	2,241	5.69	
36,301–45,800	5,564	7.06	2,806	7.12	2,758	7.00	
45,801–57,800	1,776	2.25	994	2.52	782	1.99	
57,801–72,800	1,956	2.48	1,083	2.75	873	2.22	
≧72,801	1,758	2.23	982	2.49	776	1.97	
CCI scores[4]							<0.001
0	12,839	16.30	2,536	6.44	1,814	4.61	
1	30,806	39.11	31,230	79.30	26,592	67.52	
2	27,624	35.07	4,231	10.74	7,901	20.06	
≧3	7,499	9.52	1,387	3.52	3,077	7.81	
HTN[5]							<0.001
No	54,466	69.15	29,858	75.81	24,608	62.48	
Yes	24,302	30.85	9,526	24.19	14,776	37.52	
Dyslipidemia							<0.001
No	70,086	88.98	36,527	92.75	33,559	85.21	
Yes	8,682	11.02	2,857	7.25	5,825	14.79	
RA [5]							<0.001
No	78,026	99.06	38,844	98.63	39,182	99.49	
Yes	742	0.94	540	1.37	202	0.51	

[1] Used Chi-square test to exam the characteristics distribution.
[2] Variables for propensity score matching.
[3] Patients without salary income.
[4] The CCI score calculated not including DM and DM with end-organ damage.
[5] Abbreviations: DM, diabetes mellitus; HTN, Hypertension; RA, Rheumatoid arthritis.

higher risk for periodontitis. Patients with HTN had no higher risk for periodontitis (aHR = 0.96, 95% CI = 0.92–1.00), but patients with dyslipidemia and RA both had a higher risk for periodontitis (aHR = 1.26, 95% CI = 1.19–1.34; aHR = 1.41, 95% CI = 1.19–1.67).

4. Discussion

Our study demonstrated that patients with DM have a higher risk for periodontitis compared with patients without DM based on the NHIRD database. Our study confirmed that DM is associated with periodontitis. The mechanism underlying the association of periodontitis and DM is not clear. However, investigating the mechanism relating the link between these two chronic diseases, several studies have been focused on microbial flora of the dental plaque which is the primary etiologic agent of the periodontal disease [10]. In the case of patients with DM, the concentration of oral microbial flora is increased due to a higher concentration of glucose in saliva and crevicular fluid [10]. All the evidences regarding the biologic link between DM and periodontal disease supports DM and persisting hyperglycemia leading to an exaggerated immune-inflammatory response to the periodontal pathogens [11], resulting in more rapid and severe periodontal tissue destruction. One study evaluated the association between type 2 DM and the risk of periodontitis, after 20 years follow-up period indicated that men with type 2 DM showed a 29% (HR = 1.29; 95% CI: 1.13–1.47) increased risk of periodontitis compared to those without type 2 DM [12]. Another *meta*-analysis research included studies with a total of 5724 participants including 624 cases, showed that periodontitis was associated with an increased risk of gestational DM by 66%

Table 2 – Covariates associated with periodontitis with univariate analysis.

Variables	Total	Patients without Periodontitis		Patients with Periodontitis		p-value[1]
	N	N	%	N	%	
Total	78,768	63,598	80.74	15,170	19.26	
DM[3]						0.033
No	39,384	31,681	80.44	7,703	19.56	
Yes	39,384	31,917	81.04	7,467	18.96	
Gender						0.033
Female	37,554	30,439	81.05	7,115	18.95	
Male	41,214	33,159	80.46	8,055	19.54	
Age (years)		58.52 ± 15.34		55.03 ± 12.77		<0.001
20–40	9,018	7,272	80.64	1,746	19.36	
41–54	25,504	19,634	76.98	5,870	23.02	
55–64	18,926	14,836	78.39	4,090	21.61	
≧65	25,320	21,856	86.32	3,464	13.68	
Monthly insured income (NTD.)						<0.001
≦17,280	14,101	11,487	81.46	2,614	18.54	
Dependents[2]	19,738	16,269	82.42	3,469	17.58	
17,281–22,800	24,454	20,396	83.41	4,058	16.59	
22,801–28,800	4,762	3,617	75.96	1,145	24.04	
28,801–36,300	4,659	3,642	78.17	1,017	21.83	
36,301–45,800	5,564	4,251	76.40	1,313	23.60	
45,801–57,800	1,776	1,323	74.49	453	25.51	
57,801–72,800	1,956	1,391	71.11	565	28.89	
≧72,801	1,758	1,222	69.51	536	30.49	
CCI scores[3]						<0.001
0	12,839	8,374	70.57	4,465	29.43	
1	30,806	25,859	67.39	4,947	32.61	
2	27,624	24,105	76.80	3,519	23.20	
≧3	7,499	5,260	85.24	2,239	14.76	
HTN[4]						<0.001
No	54,466	43,577	80.01	10,889	19.99	
Yes	24,302	20,021	82.38	4,281	17.62	
Dyslipidemia						<0.001
No	70,086	56,837	81.10	13,249	18.90	
Yes	8682	6761	77.87	1,921	22.13	
RA[4]						0.001
No	78,026	63,033	80.78	14,993	19.22	
Yes	742	565	76.15	177	23.85	

[1] Used Chi-square test to exam the characteristics distribution.
[2] Patients without salary income.
[3] The CCI score calculated not including DM and DM with end-organ damage.
[4] Abbreviations: DM, diabetes mellitus; HTN, Hypertension; RA, Rheumatoid arthritis.

(odds ratio [OR] = 1.66, 95% CI: 1.17–2.36). This Meta-analysis also indicated that adjusted for potential confounders estimated more than 2-fold increased odds of gestational DM among women with periodontitis (adjusted OR = 2.08, 95% CI: 1.21–3.58) [13].

The periodontal status was mainly due to oral hygiene behavior. Interestingly, periodontitis had a documented higher prevalence in men (~57%) compared to women (~39%), signifying a possible gender bias in disease pathogenesis [14–16]. Important contributing disease factors, such as DM and smoking, did not seem to significantly differ between genders, as the prevalence of DM was 9.8% in men and 9.2% in women, whereas the prevalence of smoking was 18.8% in men and 14.8% in women [17]. Our study also found that the number of male patients with periodontitis is greater than female patients. The result of our study is similar to other previous studies.

One study indicated that the risk of periodontitis increase with the advancing age that is why the high prevalence of periodontitis is seen among elderly population [18]. Another research identified that age is associated with periodontitis, and clinical attachment loss was significantly higher among individuals aged 60–69 years compared with group of adults 40–50 years [19]. Our study finds that 41–64 years old patients had a higher risk for periodontitis compared with 20–40 years old patients, but the risk for periodontitis is lower in ≧65 years old patients. Moreover, a previously study investigated the validity of CCI as a predictor of periodontitis,

Table 3 – Risk of periodontitis in DM patients with multivariable analysis of Cox model.

Variables	Adjusted-HR	95% CI	p-value
DM [2]			
No (ref.)	1		
Yes	1.04	1.01–1.08	0.029
Gender			
Female (ref.)	1		
Male	0.97	0.94–1.02	0.109
Age (year)			
20–40 (ref.)	1		
41–54	1.24	1.16–1.31	<0.001
55–64	1.18	1.10–1.26	<0.001
≧65	0.75	0.70–0.80	<0.001
Monthly insured income (NTD.)			
≦17,280 (ref.)	1		
Dependents [1]	0.97	0.92–1.03	0.374
17,281–22,800	0.85	0.81–0.90	<0.001
22,801–28,800	1.16	1.07–1.26	0.001
28,801–36,300	1.02	0.94–1.11	0.600
36,301–45,800	1.13	1.05–1.22	0.002
45,801–57,800	1.27	1.13–1.43	<0.001
57,801–72,800	1.47	1.32–1.63	<0.001
≧72,801	1.58	1.42–1.77	<0.001
CCI score [2]			
0 (ref.)	1		
1	1.08	1.00–1.17	0.044
2	0.99	0.91–1.09	0.887
≧3	0.70	0.63–0.79	<0.001
HTN[3]			
No (ref.)	1		
Yes	0.96	0.92–1.00	0.232
Dyslipidemia			
No (ref.)	1		
Yes	1.26	1.19–1.34	<0.001
RA[3]			
No (ref.)	1		
Yes	1.41	1.19–1.67	<0.001

[1] Patients without salary income.
[2] The CCI score calculated not including DM and DM with end-organ damage.
[3] Abbreviations: DM, diabetes mellitus; HTN, Hypertension; RA, Rheumatoid arthritis.

showed that CCI in elderly comorbid participants was correlated with the presence of PD [20]. Our study also found that the CCI score is associated with periodontitis.

Chronic periodontal disease (PD) is a bacteria-induced chronic inflammatory disease. Previous studies demonstrated that the influence of oral status on general health, it is only in recent decades that the association between periodontal diseases and systemic conditions [5,21]. Comorbidities may act as risk factors for PD, and PD can simultaneously be a risk indicator or risk factor for these comorbid conditions [21].

Hypertension, dyslipidemia and rheumatoid arthritis are the major diseases that related with periodontitis. The chronic inflammatory process of periodontitis and the host response provide the basis for the hypothetical association between periodontitis and cardiovascular diseases (CVD). Many cross-sectional studies documented an association between HTN and periodontitis [22,23]. Our study showed that patients with HTN could not find that had a higher risk for periodontitis. However, more well-designed prospective population trials need to be carried out to ascertain the role of periodontitis in HTN. Periodontitis and CVD may share common risk factors, and the association between periodontitis and coronary heart disease may be due to the elevated levels of plasma lipids. Epidemiological and clinical studies have also suggested that there is a relationship between periodontitis and impaired lipid metabolism [24]. Our study also revealed that patients with dyslipidemia could find that had a higher risk for periodontitis. Periodontitis and RA are immunoinflammatory diseases where leukocyte infiltration and inflammatory mediators induce alveolar bone loss, synovitis, and joint destruction, respectively. One review article confirmed that there is a correlation between periodontitis and RA. This article indicated that bacteria influence in the pathogenesis of RA and the presence of citrullinated proteins, autoantibodies, or rheumatoid factor in patients with periodontitis and RA, also demonstrated that the periodontal treatment influenced the severity of RA and periodontal clinical parameters [25,26]. Our study also revealed that patients with RA could find that had a higher risk for periodontitis.

Strengths of the study are that it was based on a large and representative population cohort, extracted from the NHI system covering 99% population in Taiwan, avoiding bias from selection, non-response, or poor recall. The NHIRD has been shown to have good levels of accuracy and completeness in recording prescriptions and clinical diagnoses. Besides, we not only adjusted for many potential confounding factors but also used the propensity score matching to select control group. Therefore, the study indicates that DM is associated with periodontitis, with a narrower and statistically significant confidence interval.

There are a few limitations in the study. The database from NHI only can present health insurance declaration information, and self-pay medical information cannot be obtained. Many factors affecting the complications of DM cannot be obtained from the NHIRD. For example, life-related variables from these patients cannot be included in the analysis, such as BMI, alcohol consumption and tobacco consumption behavior, dietary habits, etc. These factors will affect the risk of developing periodontitis. Moreover, the medications, such as antihypertensive, hypolipidemic and anti-inflammatory agents, may affect periodontitis. The medication is the confounding factor really extremely to control, especially in the retrospective cohort study. Each patient in the study period may receive inconsistent prescription patterns in the follow-up period, including drug type, drug dose, and medication duration. Therefore, our study reduced the medication confounding by adjusted comorbidity disease. In addition, the severity of DM and the disease duration of DM may also affect to periodontitis. The periodontitis is a common disease in the adult, but it is not a life-threatening disease. The incident periodontitis may be underestimated in this study. This study was a nationwide population-based study. Thus, the study results have the accuracy and representativeness. However, this study can provide evidence to prove the association between DM and periodontitis, which cannot represent the

cause-effect relation. It is necessary to obtain this information from other databases or questionnaires to conduct a prospective study to analyze the cause-effect relation between DM and periodontitis in future research.

5. Conclusions

Our study demonstrated that there is a correlation between DM and periodontitis. Patients with DM may have a higher risk of incident periodontitis compared with the patients without DM based on the NHIRD. Our study also found that the number of male patients with periodontitis is greater than the number of female patients. These patients comorbidity with HTN could not find that had a higher risk for periodontitis, while dyslipidemia and RA could find that had a higher risk for periodontitis.

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Conflicts of Interest

The authors declare no conflict of interest.

Author contributions

All authors have participated in this study and have reviewed and agree with the final manuscript. K.-H. Huang conceptualized the study; C.-Y. Lee, Y.-H. Kuan and Y.-F. Tsai developed the study methodology; C.-J. Tai and T.-H. Tsai performed the statistical analysis; C.-Y. Lee wrote the original draft; K.-H. Huang takes responsibility for the integrity of the data and the accuracy of the data analysis.

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