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Original Article

Increased risk of dry eye disease in Taiwanese patients with chronic periodontitis: A nationwide population-based cohort study

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Abstract *Background/purpose:* Dry eye disease (DED) is an extremely common ocular disease worldwide. Inflammation plays a significant role in the development and the progression of DED as well as chronic periodontitis (CP). The association between DED and CP is worth for further investigation.
Materials and methods: A retrospective cohort study was conducted by using Taiwanese Longitudinal Health Insurance Database. A total of 81996 patients who were newly diagnosed with CP from 2001 to 2012 were selected. A 1:1 propensity-matched controls without any type of periodontal diseases were selected with randomly frequency matched from the general population. The risk of DED was analyzed by Cox proportional hazards regression models, including sex, age, monthly income, urbanization, and comorbidities.
Results: CP group exhibited a significantly increased risk of DED (relative risk: 2.62, 95 % confidence interval (CI): 2.52–2.73) as compared with non-CP group. Multivariate Cox regression analysis indicated that the incidence rate of DED was significantly higher in CP group than those who in non-CP group (adjusted hazard ratio: 2.61, 95 % CI: 2.51–2.72). Female patients had a 2.09-fold higher risk of DED than male patients (95 % CI: 2.01–2.17, $P < 0.001$). The

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cumulative incidence of CP patients with DED was significantly higher than that in control subjects (log rank test, $P < 0.001$).
Conclusion: Taken together, this nationwide retrospective cohort study indicates that the risk of DED is significantly higher in Taiwanese patients with CP than in those without CP. In addition, female patients with CP are more likely to have DED.

Introduction

Dry eye disease (DED), or keratoconjunctivitis sicca, is an extremely common ocular disorder worldwide.[1,2] It is currently defined as a multifactorial disease of tear film, resulting from reduced tear production and increased tear evaporation.[2] The most well documented risk factors are elder, female, medication, and history of refractive excimer laser surgery.[2,3] In addition, the rapid aging and lifestyle changes caused by information technology have made DED as a severe public health concern.[3] In Taiwan, a nationwide population-based study has reported an increase trend in the annual incidence rates of DED from 2001 to 2015.[4]

Chronic periodontitis (CP) is related to the accumulation of bacterial biofilm resulted in host-mediated progressive destruction of both periodontal soft and hard tissues. Trends in the prevalence of periodontitis in Taiwan has been demonstrated significantly increased from 1997 to 2013.[5] Recently, studies have also shown that CP is a risk factor for many non-communicable diseases including cardiovascular diseases, chronic respiratory diseases, obesity, diabetes, and cancers.[6—10] The complex mechanisms of CP are the interactions among periodontal pathogens, inflammatory pathway, and systemic immunity leading to pocket formation, alveolar bone loss, and even tooth loss.[11]

Recently, rhegmatogenous retinal detachment, the most common type of retinal detachment in ophthalmology was reported a potential association with periodontitis.[12] From the literature review, little is known regarding the relationship between CP and DED. Therefore, we designed a nationwide population-based retrospective cohort study to investigate the possible link between CP and DED from Taiwanese National Health Insurance Research Database (NHIRD).

Materials and methods

Data source

The Longitudinal Health Insurance Database 2010 (LHID2010), the subset of NHIRD, was conducted for this nationwide population-based retrospective cohort study. LHID2010 provides scrambled patient identification number, sex, date of birth, date of visit, and the International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM) diagnostic codes. This databank contains 1 million beneficiaries randomly sampled from the 2010 registry of beneficiaries in NHIRD.[6] It has been used for many longitudinal epidemiological studies for evaluating the burden of periodontitis associated with many diseases.[7—10]

Exposure of chronic periodontitis

After approved by Chung Shan Medical University Hospital institutional review board (CS2-15071), the ambulatory patients for dental visit were identified with newly diagnosed CP (ICD-9-CM code: 523.4) from 2001 to 2012 as the CP group. The first-time CP diagnosis recognized as the index date. To ensure the accuracy of CP diagnosis, only patients with at least two outpatient service claims were captured in this study. In order to ensure the accuracy of health periodontal condition, non-CP group was randomly selected from 2000 to 2013 from participants who were never diagnosed with any type of gingivitis and periodontitis (ICD-9-CM code: 523). Propensity score of participants which predicted the probability of CP exposure for participants was estimated by logistic regression modeling. The predictors involved sex, birth year, and co-morbidities with 1:1 matched between CP and non-CP groups. Patients diagnosed as having gingivitis or periodontitis before 2001 were excluded. The flow chart of case selection and exclusion is shown in Fig. 1.

Assessment of dry eye disease

The diagnosis of DED was according to the definition of tear film insufficiency, unspecified based on the ICD-9-CM code: 375.15. All participants were followed up from index date to the date of primary outcome, withdrawal from the national health insurance system, or the end of 2013, whichever came first. In addition, we also excluded patients with comorbidities such as hypertension (ICD-9-CM code: 401—405), hyperlipidemia (ICD-9-CM code: 272.0—272.4), diabetes (ICD-9-CM code: 250), Sjögren syndrome (ICD-9-CM code: 710.2), rheumatoid arthritis (ICD-9-CM code: 714.0), and systemic lupus erythematosus (ICD-9-CM code: 710.0) to limit our study sample as DED during the observation period.

Statistical analysis

Demographic characteristics of CP and non-CP groups were analyzed by using Student's t test and Chi-square test,

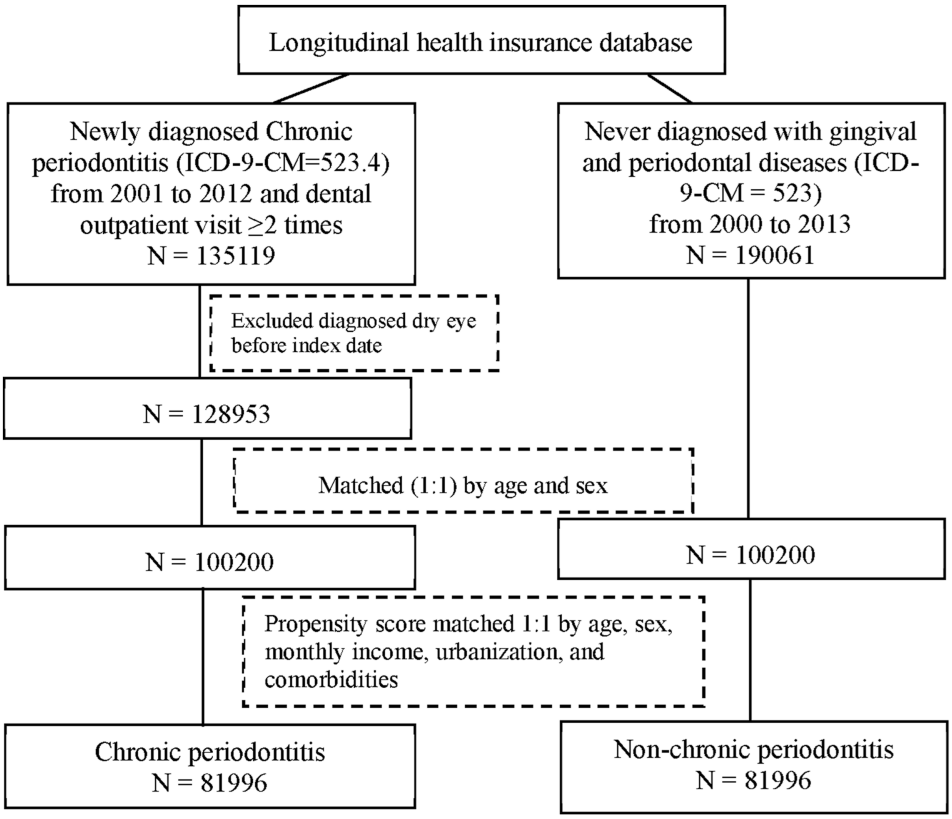

Figure 1 Flow chart of study selection procedure.

respectively. Kaplan—Meier curve was used to perform the cumulative incidence of CP and non-CP groups. In addition, log-rank test was conducted to examine the significance. Hazard ratio (HR) and 95 % confidence interval (CI) were estimated by Cox proportional hazard models. All statistical analyses were performed with SPSS version 18 (SPSS, Chicago, IL, USA). Probability levels of <0.05 were considered significant.

Results

In this study, 81996 patients with CP and 81996 subjects without CP were enrolled after propensity score matching, respectively as shown in Table 1. The demographic characteristics and selected co-morbidities were similar between CP and non-CP groups.

As shown in Table 2, the newly diagnosed DED patients were 8677 in CP group and 3336 individuals in non-CP group. The incidence density rates of DED in non-CP group was only 5.21 per 1000 person-years, but the incidence density rate was 13.66 per 1000 person-years in CP group. After Poisson regression analysis, CP group exhibited a significant risk of DED as compared to non-CP group (relative risk: 2.62, 95 % CI: 2.52—2.73).

The mean follow-up duration and time to DED between CP and non-CP groups was revealed in Table 3. The mean follow-up duration of DED was 7.7 years and 7.8 years for CP and non-CP group, respectively ($P < 0.001$). The mean time to DED was 5.1 and 5.3 years for CP and non-CP group, respectively ($P = 0.016$).

Fig. 2 demonstrates the cumulative curve of the DED incidence. The results found that the curve of CP patients was significantly higher than the curve of control subjects (log rank test, $P < 0.001$).

Cox proportional hazard model analysis for the risk of DED is shown in Table 4. After adjustment of sex, age, monthly income, urbanization, and comorbidities, CP patients showed a 2.61-fold increased risk of DED compared with non-CP controls (HR 2.61, 95 % CI: 2.51—2.72, $P < 0.001$). However, due to the lower number of systemic lupus erythematosus obtained from the baseline (Table 1), there was no significant risk for DED with systemic lupus erythematosus in the adjusted model ($P = 0.539$).

Table 5 showed the subgroup analysis of the risk of DED development. The HR of DED significantly increased in CP patients with all age subgroups compared with non-CP patients within the same age group. For age difference, P for interaction was <0.001. The HR of DED significantly increased in female as well as male CP patients compared with non-CP patients. For sex difference, P for interaction was <0.001.

Discussion

This is the first nationwide population-based retrospective cohort study to evaluate the association between CP exposure and DED risk up to 13-years follow-up period. The findings revealed a significantly higher risk of DED in patients with CP exposure than those who never received a diagnosis of CP. In addition, female patients with CP

Table 1 Demographic characteristics of chronic periodontitis group and non-chronic periodontitis group.

	Before PSM			After PSM		
	Chronic periodontitis (N = 100200)	Non-chronic periodontitis (N = 100200)	ASD	Chronic periodontitis (N = 81996)	Non-chronic periodontitis (N = 81996)	ASD
Age			0.000			0.018
<18	8979 (9.0)	8979 (9.0)		8523 (10.4)	8341 (10.2)	
18–64	81631 (81.5)	81631 (81.5)		65662 (80.1)	66212 (80.8)	
≥65	9590 (9.6)	9590 (9.6)		7811 (9.5)	7443 (9.1)	
Mean ± SD	40.1 ± 17.0	40.1 ± 17.0	0.000	39.8 ± 17.0	39.1 ± 17.4	0.040
Sex			0.000			0.007
Female	44677 (44.6)	44677 (44.6)		37608 (45.9)	37338 (45.5)	
Male	55523 (55.4)	55523 (55.4)		44388 (54.1)	44658 (54.5)	
Monthly income			0.390			0.013
<NT $25,000	64982 (64.9)	81018 (80.9)		62382 (76.1)	62838 (76.6)	
NT $25,000–NT $40,000	13188 (13.2)	9760 (9.7)		9990 (12.2)	9736 (11.9)	
>NT $40,000	22030 (22.0)	9422 (9.4)		9624 (11.7)	9422 (11.5)	
Urbanization			0.299			0.006
Urban	66248 (66.1)	52597 (52.5)		51131 (62.4)	51235 (62.5)	
Suburban	27804 (27.7)	35674 (35.6)		24912 (30.4)	24937 (30.4)	
Rural	6148 (6.1)	11929 (11.9)		5953 (7.3)	5824 (7.1)	
Hypertension	10842 (10.8)	8358 (8.3)	0.084	7712 (9.4)	7487 (9.1)	0.009
Hyperlipidemia	4977 (5.0)	2668 (2.7)	0.121	2687 (3.3)	2633 (3.2)	0.004
Diabetes	4729 (4.7)	3684 (3.7)	0.052	3598 (4.4)	3338 (4.1)	0.016
Rheumatoid arthritis	277 (0.3)	178 (0.2)	0.021	173 (0.2)	161 (0.2)	0.003
Systemic lupus erythematosus	104 (0.1)	41 (0.0)	0.023	35 (0.0)	41 (0.1)	0.003
Sjögren syndrome	140 (0.1)	34 (0.0)	0.036	28 (0.0)	34 (0.0)	0.004

PSM: propensity score matching.
ASD: absolute standardized difference.
SD: standard deviation.
N: number.
NT $: new Taiwan dollar.

Table 2 Poisson regression of relative risk of chronic periodontitis group and non-chronic periodontitis group.

	Non-chronic periodontitis	Chronic periodontitis
N	81996	81996
Person-years	640053	635227
N of dry eye disease	3336	8677
ID (95 % CI)	5.21 (5.04–5.39)	13.66 (13.38–13.95)
Relative risk (95 % CI)	Reference	2.62 (2.52–2.73)

N: number.
ID: incidence density (per 1000 person-years).
CI: confidence interval.

Table 3 Track time of chronic periodontitis group and non-chronic periodontitis group.

	Chronic periodontitis (N = 81996)	Non-chronic periodontitis (N = 81996)	*P* value
Follow-up duration (years)	7.7 ± 3.4	7.8 ± 3.3	<0.001
Time to dry eye disease (years)	5.1 ± 3.2	5.3 ± 3.3	0.016

N: number.

exhibited a higher risk of DED as compared to male patients.

Recently, Thwin et al.[13] reported a significant correlation between dry eye and periodontal disease in community-dwelling Japanese adults. However, this study was carried out only in Japanese adults residing in the Uonuma area of Niigata Prefecture that made it difficult to generalize the results of entire Japanese population. Consistently, a cross sectional study demonstrated a positive association between periodontitis and the severity of signs and symptoms related to DED in Turkey.[14] However, the sample size was small and conducted only at one university hospital, which limited the generalizability of the

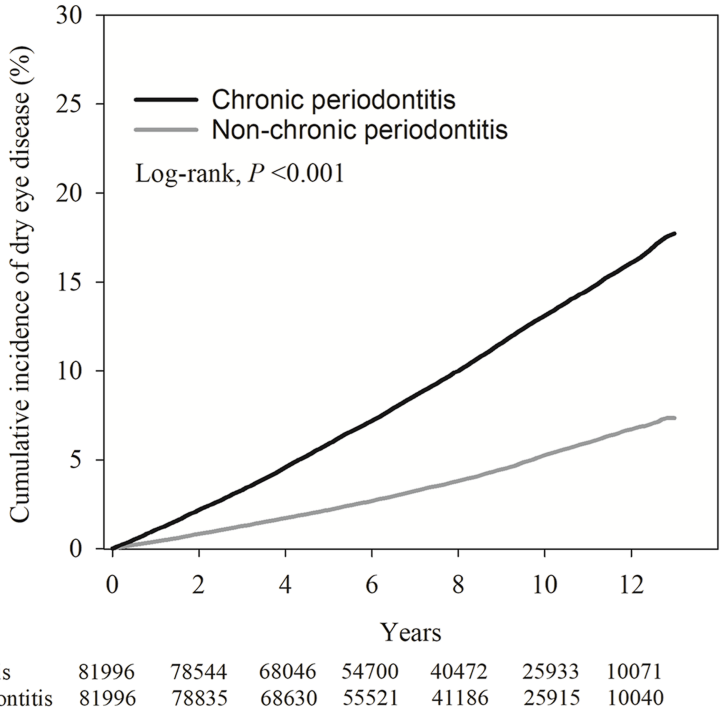

Figure 2 Kaplan—Meier plot for the cumulative incidence of dry eye disease in chronic periodontitis and non-chronic periodontitis groups.

Table 4 Cox proportional hazard model analysis for the risk of dry eye disease.

	Univariate		Multivariate[a]	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Group				
Non-chronic periodontitis	Reference		Reference	
Chronic periodontitis	2.62 (2.52—2.73)	<0.001	2.61 (2.51—2.72)	<0.001
Age				
<18	Reference		Reference	
18—64	2.11 (1.92—2.31)	<0.001	1.96 (1.79—2.15)	<0.001
≥65	4.84 (4.39—5.34)	<0.001	3.80 (3.43—4.21)	<0.001
Sex				
Male	Reference		Reference	
Female	2.04 (1.97—2.12)	<0.001	2.09 (2.01—2.17)	<0.001
Monthly income				
<NT $25,000	Reference		Reference	
NT $25,000—NT $40,000	1.00 (0.94—1.05)	0.885	1.14 (1.08—1.21)	<0.001
>NT $40,000	1.08 (1.02—1.14)	0.005	1.33 (1.26—1.41)	<0.001
Urbanization				
Urban	Reference		Reference	
Suburban	0.92 (0.89—0.96)	<0.001	0.89 (0.86—0.93)	<0.001
Rural	0.96 (0.90—1.03)	0.291	0.86 (0.80—0.93)	<0.001
Hypertension	2.37 (2.27—2.49)	<0.001	1.52 (1.44—1.61)	<0.001
Hyperlipidemia	2.46 (2.29—2.65)	<0.001	1.40 (1.29—1.51)	<0.001
Diabetes	2.33 (2.18—2.49)	<0.001	1.29 (1.20—1.39)	<0.001
Rheumatoid arthritis	2.51 (1.95—3.23)	<0.001	1.50 (1.16—1.93)	0.002
Systemic lupus erythematosus	0.91 (0.38—2.19)	0.833	0.76 (0.32—1.83)	0.539
Sjögren syndrome	6.64 (4.37—10.09)	<0.001	3.30 (2.16—5.03)	<0.001

N: number.
HR: hazard ratio.
CI: confidence interval.
NT $: new Taiwan dollar.
[a] Adjusted for age, sex, monthly income, urbanization, and comorbidities.

Table 5 Subgroup analysis for the risk of dry eye disease.

	Chronic periodontitis		Non-chronic periodontitis			
	N	N of dry eye disease	N	N of dry eye disease	HR (95 % CI)	*P* value
Age						
<18	8523	368	8341	119	2.96 (2.40—3.64)	<0.001
18-64	65662	6766	66212	2539	2.71 (2.59—2.84)	<0.001
≥65	7811	1543	7443	678	2.22 (2.03—2.43)	<0.001
					P for interaction	<0.001
Sex						
Female	37608	5365	37338	2188	2.47 (2.35—2.60)	<0.001
Male	44388	3312	44658	1148	2.91 (2.72—3.11)	<0.001
					P for interaction	<0.001

N: number.
HR: hazard ratio.
CI: confidence interval.

findings. Although the positive association between periodontal diseases and DED was observed, the risk of DED in a large, nationally representative, population-based cohort of patients with CP still needs to further investigations.

To the best of our knowledge, this study first evaluated the risk of DED stratified by follow-up years in multivariable Cox proportional hazard regression. The risk of DED was significantly higher in CP group as compared to non-CP group. Taken together, these findings indicate that the regular oral check-up as well as early detection for periodontal status are necessary for individuals with DED.

The possible mechanisms of increased risk of CP in DED patients may be associated with the shared common etiology factors including inflammatory processes, immunological reactions, risk factors, medication use, and microbial translocation.[15—17] Therefore, periodontal pathogens evoke the inflammatory cytokines and the increased levels of autoantibodies that may cause an immune invasion of the lacrimal gland and disrupt its functions.[18,19] In addition, aging, comorbidities, and smoking could also take part in the association between CP and DED.[20,21]

The strength of this study was the use of LHID2010 that composed the whole Taiwanese population. The cohort study design could confer a higher level of evidence to suggest a causal relationship between CP and DED. However, some potential limitations should be addressed. First, since NHRID is diagnosis and treatment based, the laboratory data are unavailable. Therefore, the severity of CP as a risk factor for developing DED could not be further evaluated. Second, the lack of some lifestyle information and physical examination in LHID2010 might also be a bias to the analytical results. Third, due to this is a register-based study, the unrecognized periodontitis patients who did not have dental medical claims might be included in the healthy controls through the study design. Only people with DED who had been diagnosed by an ophthalmologist were enrolled, the DED population in this study may be underestimated. By using propensity score matching could minimize the selection bias and avoid the confounding variates.

The findings of this nationwide, population-based cohort study revealed a significant association between CP exposure and DED risk. Regular check-up, early detection, and effective management of both CP and DED are strongly recommended for the cooperation between dentist and ophthalmologist. In addition, further prospective clinical studies on the relationship between CP and DED are warranted.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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