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Periodontitis exposure within one year before anti-diabetic treatment and the risk of rheumatoid arthritis in diabetes *mellitus* patients: a population-based cohort study

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ABSTRACT

Objective: To examine whether a history of periodontitis (PD) before anti-diabetic treatment is associated with risk of rheumatoid arthritis (RA) development in newly-treated diabetes *mellitus* (DM) patients.

Methods: We conducted a population-based retrospective cohort study using the 1997-2009 National Health Insurance (NHI) claims data of one million representative individuals from all NHI enrollees. Adults with DM (aged ≥20 years) starting anti-diabetic treatment during 2001–2009 were classified as newly-treated DM patients. We identified 7097 DM subjects with PD history within one year before initiating anti-diabetes treatment (index date). By matching these 7097 subjects for age on the index date, sex, and year of the index date, we randomly extracted 14,194 DM subjects without PD history within one year before anti-diabetic treatment. Adjusted hazard ratios (aHRs) with a 95% confidence interval (CI) were calculated by applying Cox proportional hazards models to quantify the association between PD history and RA risk.

Results: Compared with DM patients without PD exposure within one year before anti-diabetic treatment, crude HR and adjusted HR of RA among DM patients with PD exposure within one year before anti-diabetic treatment were 4.51 (95% CI, 1.39–14.64) and 3.77 (95% CI, 1.48–9.60).

Conclusion: PD exposure within one year before anti-diabetic treatment was associated with increased RA risk in newly treated DM patients. The lack of knowledge about individual smoking status is a major limitation of this study.

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Exposição à periodontite no intervalo de um ano antes do tratamento antidiabético e risco de artrite reumatoide em pacientes com diabete mellitus: estudo de coorte populacional

R E S U M O

Palavras-chave:
Diabetes *melittus*
Periodontite
Artrite reumatoide
Risco
Banco de dados administrativos

Objetivo: Examinar se uma história de periodontite (PD) antes do tratamento antidiabético está associada a risco de ocorrência de artrite reumatoide (AR) em pacientes com diabetes *melittus* (DM) tratados *de novo*.

Métodos: Fizemos um estudo retrospectivo populacional com os dados de reivindicações do *National Health Insurance* (NHI) de 1997-2009 referentes a um milhão de indivíduos representativos da totalidade de matriculados. Adultos com DM (≥ 20 anos) que iniciaram o tratamento antidiabético durante 2001-2009 foram classificados como pacientes DM tratados *de novo*. Identificamos 7.097 indivíduos DM com história de PD em um intervalo de um ano antes do tratamento antidiabético (data-índice). Na equiparação desses 7.097 indivíduos para idade por ocasião da data-índice, gênero e ano da data-índice, extraímos aleatoriamente 14.194 pacientes DM sem história de PD em um intervalo de um ano antes do tratamento antidiabético. As razões de risco ajustadas (aRR) com um intervalo de confiança (IC) de 95% foram calculadas mediante a aplicação do modelo de riscos proporcionais de Cox com o objetivo de quantificar a associação entre história de PD e risco de AR.

Resultados: Em comparação com pacientes DM sem exposição à PD no intervalo de um ano antes do tratamento antidiabético, RR bruta e RR ajustada para AR entre pacientes DM e com exposição à PD no intervalo de um ano antes do tratamento antidiabético foram, respectivamente, 4,51 (IC 95%, 1,39-14,64) e 3,77 (IC 95%, 1,48-9,60).

Conclusão: A exposição à PD no intervalo de um ano antes do tratamento antidiabético foi associada a maior risco de AR em pacientes DM tratados *de novo*. A ausência do *status* de tabagismo em nível individual é importante limitação desse estudo.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic synovial inflammation with periarticular osteoporosis and bone erosion, associated with an increased risk of cardiovascular disease comparable to that of diabetes mellitus (DM).[1] Although the exact etiology is still unknown, the interaction between environmental factors and genetic factors has been found to play a role in RA pathogenesis.[2] Smoking is a well-known risk factor,[3-10] and recently periodontitis (PD) has emerged as another environmental risk factor for RA.[11,12] PD is a common chronic, microbially triggered an inflammatory disorder that causes an irreversible loss of the supporting tooth structures, and may ultimately lead to tooth loss.[13] It affects approximately half of the population aged ≥ 30 years in the United States.[14,15] One of the major PD-related pathogens, *Porphyromonas gingivalis* (*P. gingivalis*), is the only microorganism that produces peptidylarginine deiminase, which may cause citrullination.[16] In genetically susceptible individuals, the breakdown of immune tolerance to citrullinated peptides may lead to the production of anti-cyclic citrullinated peptide (anti-CCP) antibodies, associated with RA development.[17] The presence of *P. gingivalis* DNA in the serum and synovial fluid and a strong correlation between the presence of anti-CCP antibodies and the presence of PD in RA patients support this hypothesis.[18-20]

In recent years, increasing evidence has indicated a bidirectional association between DM and PD.[21,22] PD is associated with increased incident DM risk, poor glycemic control, and DM complications,[23-26] probably due to the higher levels of systemic proinflammatory mediators that exacerbate insulin resistance.[22] A number of observational studies also show a greater prevalence, severity, extent, or progression of one or more PD indicators in DM patients, with type 1, type 2, or gestational diabetes, as compared to those in non-DM subjects.[27-35]

Hyperglycemia has been found to modify PD expression,[36] by interfering with the host response and causing an excessive inflammatory response to infection,[37,38] as well as by the interaction of the receptor for advanced glycation end products (RAGE) with its ligands in gingiva.[22,36,39] Several previous studies have shown that DM patients have defective neutrophil function,[40-42] which may lead to impaired clearance of *P. gingivalis*, the major periodontal bacterium related to RA pathogenesis.[17] In diabetic mice, inoculation with *P. gingivalis* leads to prolonged and exaggerated systemic cytokine expression and inflammatory infiltrates in a model of calvarial infection.[37,38] Hence, we hypothesize that the prolonged challenge presented by the oral bacteria as a result of the defective host response, together with the exaggerated and sustained inflammatory response to the bacteria, may cause more severe PD in DM subjects than in non-DM subjects with PD. Recent studies show a dose-dependent association between PD exposure and RA risk.[11,12] Because hyperglycemia is present for some time before commencing anti-diabetic treatment in DM patients,[43] we hypothesize that among newly-treated DM patients, those who had PD exposure within one year before

anti-diabetic treatment may have a higher risk of RA development than those without PD exposure within one year before anti-diabetic treatment.

To the best of our knowledge, no population-based cohort study has examined whether RA risk differs between newly-treated adults with and without a history of PD before anti-diabetic treatment. Recently, the Taiwanese National Health Insurance Research Database (NHIRD) had facilitated population-based longitudinal studies. We therefore took advantage of this resource to conduct this cohort study to estimate the hazard ratios (HRs) for the association between PD history and RA development in newly-treated DM patients.

Methods

Data source

The source of data was the NHIRD, which covered claims of ambulatory care, inpatient services and dental services, and prescriptions during 1997-2009. In March 1995, the National Health Insurance (NHI) program was implemented, and it has since covered more than 98% of the population. The National Health Research Institute, which manages the NHIRD, has released comprehensive NHI-related administrative claims data for research. In 2000, the NHIRD randomly selected one million participants to form a representative database for study purposes. Here we used one million representative subjects from the multiple datasets of the NHIRD: ambulatory and inpatient claims files, enrollment files, and the NHI catastrophic illness files, all from 1997-2009. The NHI catastrophic illness files were established to track patients with major or catastrophic illnesses, including cancer, end-stage renal disease, mental illness, congenital illness, and several autoimmune diseases, including RA. The Bureau of National Health Insurance (BNHI) routinely reviews the original medical charts of all patients who applied for catastrophic illness registration to validate the diagnoses. The American College of Rheumatology classification criteria for RA (1987) was used to validate RA diagnosis for the period 1997–2009.[44] The ambulatory and inpatient files include information on date of visit/admission, diagnoses, examinations, procedures, and medical expenses. The enrollment files provide enrollment and demographic information. Although the dataset lacked laboratory and radiographic data, the BNHI periodically audited the accuracy of diagnoses by randomly sampling patient charts to check claims.[45] The Ethics Committee of Clinical Research at Taichung Veterans General Hospital approved this study.

Study samples

DM subjects
In this retrospective cohort study, we identified patients who had at least one diagnosis of DM [International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 250×] with concurrent prescription of any anti-diabetes medication for more than 28 days after January 1, 2001 and classified these as DM subjects.

Subjects with and without PD history
In Taiwan, BNHI covers the cost of dental scaling a maximum of twice per year for each individual, with the aim of improving dental health. For these patients, dentists may perform scaling for these people with a concurrent PD coding (ICD9-CM codes 523.3–5). Therefore, we defined PD exposure as having a diagnosis of PD (ICD9-CM codes 523.3–5) together with concurrent antibiotic therapy, or with periodontal treatment other than dental scaling by certified dentists. PD history was defined as having PD during the one year before the index date. Patients who had not been diagnosed with periodontal disease (ICD9-CM Codes 523×) within one year before the index date were classified as patients with no PD history.

Exclusion criteria
All individuals diagnosed with RA (ICD9-CM code 714.0) before the index date or aged younger than 20 years on the index date were excluded.

Matched study subjects
The first date of anti-diabetic treatment was defined as the index date. First, we identified a total of 7097 DM subjects with PD history. To match these DM subjects with PD history in terms of age on the index date (i.e., 20–34, 35–49, 50–64, ≥ 65 years), sex, and the year of the index date, we randomly selected 14,194 DM subjects with no PD history.

Outcome variable
Patients who had ambulatory visits coded for RA (ICD9-CM Code 714.0) and certificates of the catastrophic illness for RA were classified as RA cases. The outcome variable was the time (in years) from the index date to the date of their first ambulatory care visit with a concurrent RA diagnosis. If the study subjects withdrew from the Taiwanese NHI system for any reason, such as death or moving away, the date of withdrawal was selected as the censored date, otherwise the last date of the dataset (December 31, 2009) was used.

Potential confounders
The study included the insurable wage and urbanization level of the study subjects as potential confounders. In Taiwan, the insurable wage was calculated from the average monthly income of the participants, which served as an economic index. If the insurable earnings of the subject was zero, the insurable wage was treated as dependence. The insurable wage was converted from new Taiwan dollars (TWD) to USD using a conversion rate of 30 TWD to 1 USD. The insurable wage was transferred to ordinal variables (i.e., dependence, 1–700 USD and > 700 USD). We selected 700 USD as the cut-off value for insurable wage because it was the median of the insurable wages among subjects whose insurable earnings were not zero. Based on the previously stratified seven clusters [from level 1 (most urbanized) to level 7 (least urbanized), in Taiwan,[46] the urbanization level was converted into 3 levels: urban (levels 1–2), suburban (levels 3–4), and rural (levels 5–7).

Statistical analysis

We compared baseline characteristics based on PD history using a t-test for continuous variables, and Pearson's χ^2 or

Fisher's exact test for categorical variables. Adjusting for age, sex, insurable wage and urbanization level of subjects, Cox proportional regression analysis was used to estimate incident RA risk associated with PD history, as shown by adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). A two-tailed P-value of < 0.05 was considered statistically significant. All statistical calculations were performed using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL).

Sensitivity analysis

We conducted lag analyses by advancing the RA diagnosis date by 3 months, 6 months, and 1 year and examined the potential impact of insidious RA onset. We then repeated the Cox proportional regression analyses after excluding those whose follow-up time was less than 3 months, 6 months, or 1 year, and subtracting the follow-up time by 3 months, 6 months and 1 year respectively, as the revised follow-up time.

Results

A total of 21,291 DM subjects were followed for a median (interquartile range) of 3.4 (1.5, 5.9) years; of these, 19 subjects developed incident RA. The demographic and clinical data according to PD history are shown in Table 1. The mean patient age ± SD was 57.5 ± 12.8 years and women comprised 43.3% of all study subjects.

Among the 7,097 DM subjects with a history of PD exposure within one year before the index date, 12 subjects developed RA after 26,910 person/years of follow-up and the incidence was 44.6 cases per 10^5 person/years. Among the 14,194 DM subjects without PD history, 7 subjects developed RA after. From 54,002 person/years of follow-up, the incidence was 13 cases per 100,000 person/years. Compared with subjects without PD history, the crude HR of incident RA among those with PD history was 4.51 (95% CI 1.39–14.64). As shown in Table 2, after adjusting for age, sex, insurable wage, and urbanization level of the subjects, the adjusted HR (aHR) of RA associated PD history remained statistically significant (aHR, 3.77; 95% CI 1.48–9.60). The survival curve for incident RA among DM individuals is shown in Figure 1.

Table 3 shows the results of sensitivity analyses conducted by varying the lag time of RA diagnosis considering the insidious RA onset. The association between PD history and RA risk remained statistically significant after varying the lag time.

Discussion

This study is the first population-based cohort study to use administrative data to examine the strength of the association between PD history within one year before anti-diabetic treatment and RA risk in newly-treated DM patients. This study focuses on PD exposure history within one year before anti-diabetic treatment because we hypothesize that hyperglycemia may exist during this period, and thus interact

with PD to drive an increased RA risk. The main finding of our study is that the association between PD history and RA development is statistically significant among newly treated DM individuals. In addition, if the lag time of RA diagnosis is considered, this association became stronger.

The results of this cohort study further supports the theory that PD history is associated to RA development, which was also suggested by the results of two recent case–control studies.[11,12] However, the results of another large cohort study on American women indicated that PD was not associated with RA risk.[47] Of note, DM status was not taken into account in this previous cohort study, and no male subjects were included.[47]

The main strength of this study is that the use of population-based samples of Taiwanese women and men could avoid selection bias and the results should be applicable to the general population of Taiwan. Furthermore, to increase

| Table 1 – Comparison of demographic data for patients based on periodontitis (PD) history within one year before the index date in newly-treated diabetic patients.			
Variable	PD history (n = 7097)	No PD history (n = 14194)	p
Female	3074 (43.3)	6148 (43.3)	1.000
Age (years)			1.000
20–34	238 (3.4)	476 (3.4)	
35–49	1660 (23.4)	3320 (23.4)	
50–64	3121 (44.0)	6242 (44.0)	
≥ 65	2078 (29.3)	4155 (29.3)	
Urbanization level			< 0.001
Urban	2748 (38.7)	4873 (34.3)	
Suburban	2854 (40.2)	5990 (42.2)	
Rural	1495 (21.1)	3331 (23.5)	
Insurance amount (USD)			< 0.001
Dependence	440 (6.2)	894 (6.3)	
1–700	3069 (43.2)	6919 (48.7)	
>700	3588 (50.6)	6381 (45.0)	

RA, rheumatoid arthritis; DM, diabetes *mellitus*; PD history, a history of periodontitis within one year before anti-diabetic treatment.

Table 2 – Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of RA risk associated with variables in newly-treated DM patients.		
Variável	HR (95% CI)	p value
A history of PD	3.77 (1.48–9.60)	0.006
Female	6.04 (1.73–21.05)	0.005
Age, incremental year	1.04 (1.00–1.08)	0.085
Urbanization level		
Urban	Reference	-
Suburban	1.34 (0.44–4.14)	0.608
Rural	1.67 (0.50–5.54)	0.405
Insurable wage (USD)		
Dependence	Reference	-
1–700	3.35 (0.43–26.00)	0.248
> 700	1.43 (0.13–15.33)	0.767

RA, rheumatoid arthritis; DM, dabetes mellitus; PD, periodontitis; USD, United States dollar.
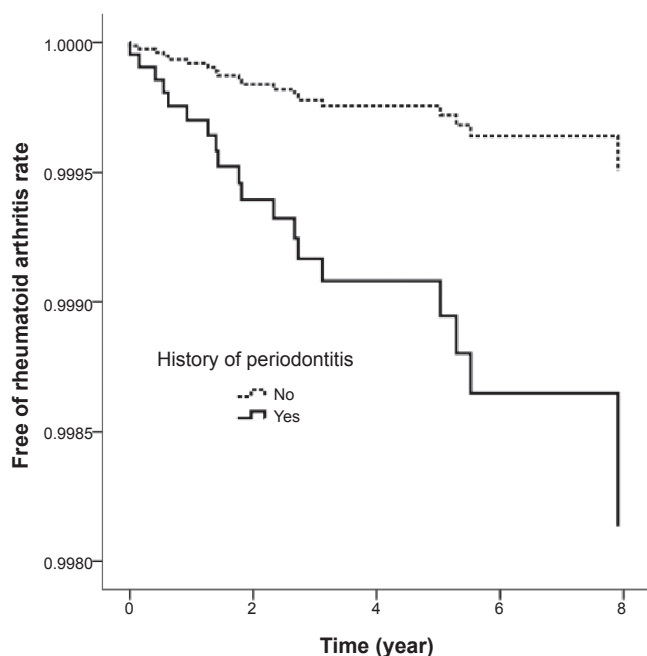
Fig. 1 – Free of incident rheumatoid arthritis rates among subjects with diabetes mellitus stratified by periodontitis history.

Lag time	PD history	No PD history	HR (95% CI)
	n, RA/total (%)	n, RA/total (%)	
No lag time	12/7097 (0.17)	7/14194 (0.05)	3.77 (1.48–9.60)
3 months	12/6801 (0.18)	5/13654 (0.04)	5.31 (1.86–15.14)
6 months	11/6529 (0.17)	5/13034 (0.04)	4.86 (1.68–14.08)
1 year	9/5918 (0.15)	4/11835 (0.03)	5.12 (1.57–16.74)

Table 3 – Sensitivity analyses for RA risk associated with PD history by varying the lag time of RA diagnosis, as shown by adjusted hazard ratios (HRs) with 95% (CIs).

RA, rheumatoid arthritis; DM, diabetes *mellitus*; PD, periodontitis; PD history, a history of periodontitis within one year before anti-diabetic treatment.
Cox regression analyses were conducted after adjusting for age, sex, urbanization level, and insurable wage of subjects.

the accuracy of diagnoses. Moreover, the non-differential misclassification of RA and PD diagnoses would have biased the results towards the null. Second, use of the NHIRD precluded further adjustment of unmeasured potential confounders, such as serum glucose level, glycated hemoglobin, anti-CCP antibodies, HLA-DRB1, and smoking status of subjects. Third, the small number of incident RA cases limits the number of covariates for adjustment. Finally, the results of this population-based study in Taiwan might not be used to generalize other ethnic populations.

Conclusion

This nonselective, population-based cohort study indicates that PD history within one year before anti-diabetic treatment is associated with increased RA risk in newly treated DM patients. Further clinical and basic studies need to be performed to elucidate whether the degree of hyperglycemia interacts with RA risk associated with PD exposure.

Authors' contributions

Dr Hsin-Hua Chen had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hsin-Hua Chen, Der-Yuan Chen, Nicole Huang, Pesus Chou.

Data acquisition: Hsin-Hua Chen, Ching-Heng Lin.

Data analysis and interpretation: Hsin-Hua Chen, Der-Yuan Chen, Shih-Yi Lin, Nicole Huang, Pesus Chou.

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Conflicts of interests

The authors declare no conflict of interest.

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internal validity, this study matched study subjects with regarding age, sex, and the year of the index date, and further adjusted potential confounders including the insurable wage and urbanization level of subjects. However, a number of limitations must be considered. First, the accuracy of diagnoses in administrative data is an area of concern. Bias due to misclassification or miscoding of PD and RA can still occur despite regular audit of the quality of claims carried out by periodically sampling patient charts, which is randomly performed by the BNHI. However, the accuracy of RA diagnosis is of less concern, because the issue of a catastrophic illness certificate for RA diagnosis requires validation by at least two qualified rheumatologists and involves checking the medical charts, radiographic findings, and laboratory data. In addition, the inclusion of periodontal treatment in the diagnostic criteria of PD also helps increase

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