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Periodontal Treatment and the Risks of Cardiovascular Disease in Patients with Type 2 Diabetes: A Retrospective Cohort Study

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Abstract

Objective Periodontal disease may predispose individuals to cardiovascular disease (CVD). Diabetes mellitus, especially in patients with severe periodontitis, increases the risk of CVD mortality. However, the outcomes of periodontal therapy vary among the different treatment modalities. We aim to investigate whether periodontal treatment could influence the occurrence of CVD in patients with type 2 diabetes and periodontal problems.

Methods A retrospective cohort study was conducted based on a dataset released by Taiwan National Health Insurance (NHI). The dataset was composed of randomly sampled, newly diagnosed diabetic patients who received insurance benefits from 1999 to 2001; patients who were younger than 18 years of age or who already had CVD before 1999 were excluded. The NHI code was used to identify the treatments, including subgingival curettage and flap operations. The patients' demographic variables were matched using a 1:4 propensity score. All of the subjects were followed up until the onset of CVD, or December 31, 2011. A Cox proportional hazards regression analysis was performed to evaluate the effects of periodontal treatment on the rates of myocardial infarction, heart failure and stroke.

Results Three thousand thirty-nine and 12,156 diabetic subjects were classified into the advanced periodontal treatment group and the non-advanced periodontal treatment group, respectively. The Cox proportional hazards analysis revealed that although the overall incidence of CVD was not significantly improved (Hazard ratio, HR 0.95; 95% CI 0.90-1.01), advanced periodontal treatment reduced the rates of myocardial infarction (HR 0.92; 95% CI 0.85-0.99) and heart failure (HR 0.60; 95% CI 0.45-0.80). There was no significance difference in the incidence of stroke (HR 0.95; 95% CI 0.85-1.06).

Conclusion Advanced periodontal therapy lowers the rate of CVD, especially myocardial infarction and heart failure. Dental management has a beneficial effect on the health of patients with type 2 diabetes.

Key words: type 2 diabetes, periodontal treatment, cardiovascular disease, myocardial infarction, heart failure, stroke

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Introduction

Periodontal disease, which is essentially a chronic infection and inflammatory condition, may predispose individuals to cardiovascular disease. Tooth loss, which is viewed as a marker of past periodontal disease, is related to the presence of subclinical carotid atherosclerotic plaque, which thereby provides a potential pathway and relationship with clinical cardiovascular disease (CVD) (1). The results of a meta-

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analysis suggest that periodontal infections increase the risk of CVD, including coronary artery disease (CAD) and cerebrovascular disease (2). Another study revealed that periodontal disease increases the risk of future CVD, which is more prominent in individuals who are younger than 65 years of age (3). During a 12-year follow-up period, men who had history of periodontal disease and fewer teeth at baseline were found to be at a higher risk of ischemic stroke (1). Kapellas et al. reported that periodontal pocketing was a marker of presymptomatic arterial dysfunction in indigenous Australians, who show a higher rate of periodontal disease and experience of CVD earlier than non-indigenous individuals (4). However, while positive evidence exists, it remains controversial whether periodontitis is associated with CAD due to the presence of numerous uncontrolled confounding factors and the different assessments of periodontal disease (5).

Using a nationwide, population-based study and a prospective cohort design, Chen et al. demonstrated that tooth scaling decreased the cardiovascular risk. A group of patients who were exposed to tooth scaling had lower rates of acute myocardial infarction (1.6% vs. 2.2%, $p<0.001$), stroke (8.9% vs. 10%, $p=0.03$), and total CVD (10% vs. 11.6%, $p<0.001$) in comparison to a non-exposed group. Furthermore, more frequent tooth scaling was correlated with a greater risk reduction (6). However, the effects of therapeutic periodontal intervention on CVD vary according to the different treatment modalities, which remain controversial and require further investigation (7).

Diabetes mellitus, which occurs worldwide, is a highly prevalent disease. It is linked with a consistent increase in mortality, which is mostly related to CAD (8). Individuals with diabetes and severe periodontitis have been found to have a significantly increased intimal-medial wall thickness, acoustic shadowing and a higher incidence of CAD in comparison to individuals without diabetes or periodontal disease (9). A prospective longitudinal study suggested that periodontal disease predicted CAD-related mortality in Pima Indians with type 2 diabetes, especially in those with severe periodontal abnormalities (10).

The Taiwan National Health Insurance (NHI) program, which has been in operation since 1995, enrolls nearly all of the inhabitants of Taiwan. Complying with national standards, this program allows beneficiaries to receive various fundamental managements, including periodontal therapy. In the present study, we aim to use a dataset released by the Taiwan NHI to investigate whether advanced periodontal treatment can reduce the occurrence of CVD in type 2 diabetic patients with periodontal disease.

Materials and Methods

Database

The NHI Research Database at the National Health Research Institute in Taiwan, which is in charge of the complete NHI claims database, released a dataset for research purposes. The present dataset is composed of 360,000 randomly sampled, newly diagnosed diabetic patients who were beneficiaries of the NHI program during 1999-2001 (120,000 subjects per year). The records of all of these individuals were collected. Each patient's original identification number was encrypted using a consistent procedure to protect his or her privacy. Hence the linkage of claims belonging to the same patient is feasible within the database. Because the present study used de-identified secondary data that were released to the public for research purposes, it was exempt from a full review and was approved by the institutional review board of Chung Shan Medical University Hospital in Taiwan (CSMUH No: CS13023). The need for consent was waived because the patients' records and information were anonymous and had been de-identified prior to the analysis.

Study sample

This is a retrospective cohort study. Patients with type 1 diabetes, gestational diabetes, or any missing data were excluded; those with periodontitis [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 523.4 and 523.5] and who were treated in the dental outpatient department (OPD) in the 3 years following their diagnosis of diabetes were recruited. We only enrolled patients with at least three entries that indicated periodontitis, in order to eliminate unnecessary entries or cases in which a dental health examination was performed. All the treatment charges were covered by the NHI program, while dentists were reimbursed according to the codes that they entered. The process of recruitment is shown in Fig. 1.

All of the selected subjects were at least 18 years of age. We excluded patients who were diagnosed with CVD in 1998 and before the observational index date, in order to ensure the likelihood that only new cases of CVD would be identified (ICD-9-CM codes, 410-447), including CAD (myocardial infarction) (ICD-9-CM codes 410-414), heart failure (ICD-9-CM code 428), and stroke (ICD-9-CM codes 431-435). We used the NHI Bureau codes for the treatment procedures to identify the periodontal treatment procedures. Subgingival curettage and flap operations, which are applied to cure the inflammation of deep pockets, were defined as advanced periodontal treatments. Subgingival curettage is indicated for periodontitis in patients with pockets of ≥5 mm in depth after ultrasonic calculus removal. The diagnosis is made using an X-ray image and by measuring the pocket depth. The disease is managed with subgingival curettage and root planning (91006C, 91007C and 91008C for full-mouth, half arch and one-third arch subgingival curettage, respectively). A flap operation is indicated for periodontitis in patients with pockets of ≥5 mm in depth and who present discharge tinged with blood or pus at one month after subgingival curettage. A diagnostic study includes a full-mouth pocket depth measurement and X-ray examination. After obtaining informed consent to perform the operation, the flap

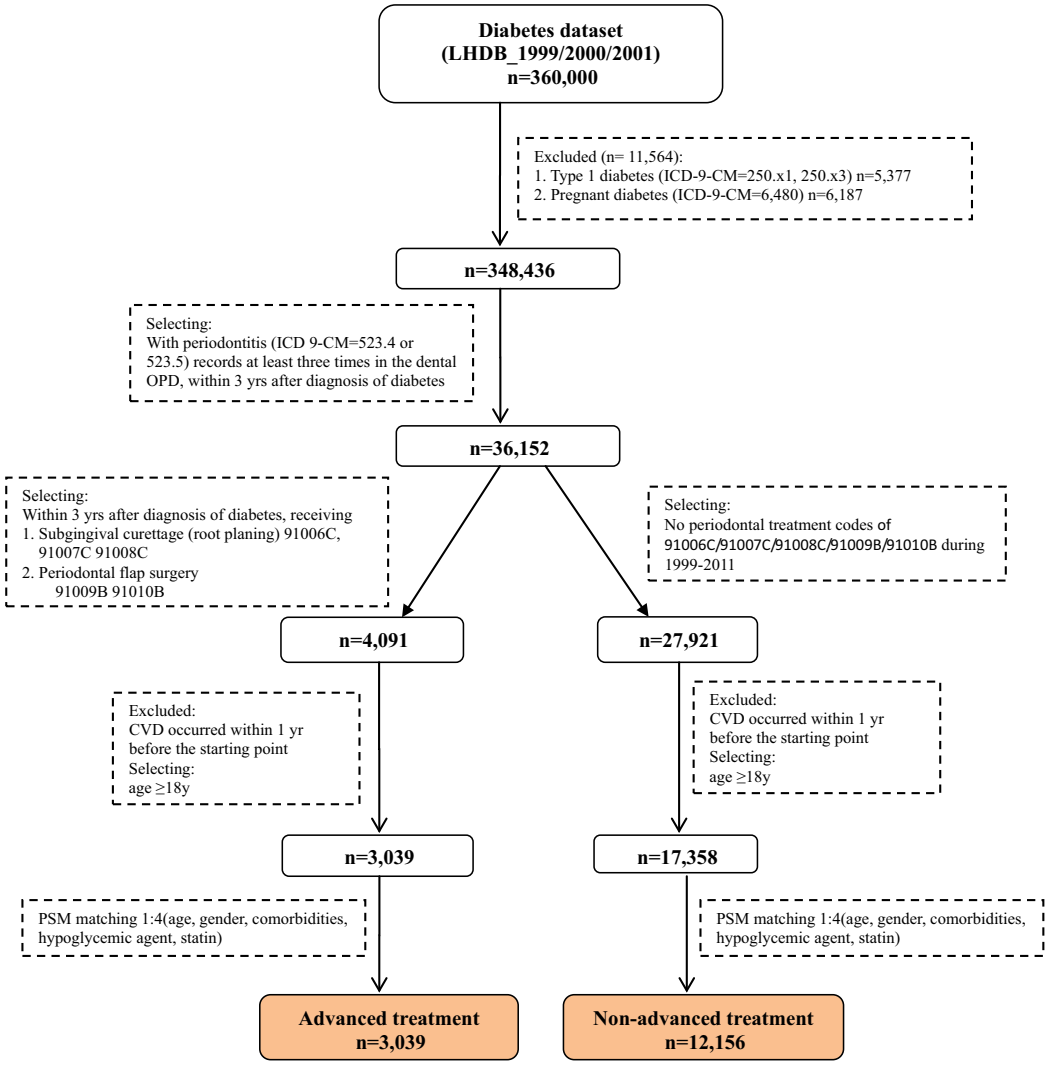

Figure 1. **The flow chart illustrates the selection and division of the advanced treatment and non-advanced treatment groups. OPD: out-patient department, PSM: propensity-score matching**

operation is administered to remove the granulation tissue, remodel the alveolar bone, and reduce the pocket depth (91009B for local flap operation and 91010B for one-third arch flap operation). The subjects were grouped according to the most severe periodontal therapy that they had undergone. Those with periodontal problems who received dental therapies other than the above-mentioned advanced periodontal treatments were defined as the non-advanced periodontal treatment group.

1:4 propensity-score matching was performed between the advanced-treatment and non-advanced-treatment groups. The following variables were matched to balance known risk factors across the groups: age, gender, comorbidities, hypoglycemic agents, and statins. All of the patients were followed up until the onset of CVD or December 31, 2011. The sensitivity and specificity of the identification of events using ICD-9-CM in the National Health Research Insurance database in comparison to a direct chart review were 100% and 95%, respectively (11).

Statistical analysis

We used the IBM SPSS software program (version 18.0, SPSS, Chicago, USA) for the statistical analysis. All of the data were expressed as the frequency (percentage) or the mean standard deviation. The parametric continuous data between the advanced-treatment and non-advanced-treatment groups were compared using the unpaired Student's *t*-test. A Cox proportional hazards regression analysis was carried out to evaluate whether periodontal treatment was an independent factor in determining the occurrence of CVD, myocardial infarction, heart failure, and stroke. Potential risk factors, including age, the administration of oral hypoglycemic agents or statins and the presence of comorbidities were incorporated into the model. Two-sided p values of <0.05 were considered to indicate statistical significance.

Results

The demographic data are shown in Table 1. The selection of the recruited patients before propensity-score match-

Table 1. Demographic Data of Study Population.

	Unmatched					Matched				
	Advanced treatment (n=3,039)		Non-advanced treatment (n=17,358)			Advanced treatment (n=3,039)		Non-advanced treatment (n=12,156)		
	No.	%	No.	%	p value	No.	%	No.	%	p value
Age					<0.001**					0.758
18-45	720	23.7	4,554	26.2		720	23.7	2,805	23.1	
45-64	1,849	60.8	9,406	54.2		1,849	60.8	7,472	61.5	
≥65	470	15.5	3,398	19.6		470	15.5	1,879	15.5	
mean ± SD	53.1±10.7		53.0±12.9		0.812	53.1±10.7		53.1±10.7		0.983
Gender					<0.001**					1
Female	1,217	40.0	7,999	46.1		1,217	40.0	4,868	40.0	
Male	1,822	60.0	9,359	53.9		1,822	60.0	7,288	60.0	
Biguanides	1,472	48.4	7,785	44.8	<0.001**	1,472	48.4	5,821	47.9	0.586
Sulfonylurea	1,496	49.2	8,475	48.8	0.683	1,496	49.2	6,330	52.1	0.005**
Alpha-glucosidase inhibitors	383	12.6	1,818	10.5	<0.001**	383	12.6	1,383	11.4	0.059
Thiazolidinediones	485	16.0	2,268	13.1	<0.001**	485	16.0	1,722	14.2	0.012*
Glinides	229	7.5	1,099	6.3	0.013*	229	7.5	821	6.8	0.129
DPP-4 inhibitors	214	7.0	826	4.8	<0.001**	214	7.0	626	5.1	<0.001**
Insulin and analogues	146	4.8	885	5.1	0.494	146	4.8	632	5.2	0.377
Statin	808	26.6	4,301	24.8	0.034*	808	26.6	3,173	26.1	0.586
Hypertention	1,678	55.2	9,471	54.6	0.505	1,678	55.2	6,828	56.2	0.343
Chronic liver disease	565	18.6	3,429	19.8	0.136	565	18.6	2,467	20.3	0.036*
COPD	211	6.9	1,545	8.9	<0.001**	211	6.9	1,022	8.4	0.008**
Renal disease	90	3.0	639	3.7	0.049*	90	3.0	426	3.5	0.139
Mental disorder	334	11.0	1,957	11.3	0.648	334	11.0	1,348	11.1	0.877
Cancer	106	3.5	558	3.2	0.433	106	3.5	381	3.1	0.322

*p<0.05, **p<0.01

ing showed that CVD occurred before entry in 25.7% (1,052/4,091) of the patients in the advanced periodontal treatment group and 37.8% (10,563/27,921) of the patients in the non-advanced periodontal treatment group. These patients were excluded from the study. It seems that there was a slightly increased rate of CVD among the patients in the non-advanced periodontal treatment group within 1 year before the starting point. One possible explanation is that some patients with CVD might pay more attention to their CVDs rather than their periodontal condition and thus may only receive non-advanced periodontal treatment for their periodontal problems. This might be why more patients with CVD were found in the non-advanced periodontal treatment group before exclusion. After 1:4 propensity-score matching, 3,039 and 12,156 diabetic subjects were retained in the advanced periodontal treatment group and the non-advanced periodontal treatment group, respectively. After the matching of the two groups, there were no differences in terms of age or gender; however, differences remained with respect to the patients' medical prescriptions, such as sulfonylurea, thiazolidinediones, and dipeptidyl peptidase 4 (DPP-4) inhibitors, and in the presence of co-morbidities such as chronic liver disease and chronic obstructive pulmonary disease (COPD).

The occurrence of CVD and the hazard ratios (HRs) of the risk factors are shown in Table 2. After adjusting for confounding variables, advanced periodontal treatment was found to have a neutral effect on the incidence of CVD in diabetic patients. Older patients had a higher HR, especially those who were ≥65 years of age. All of the prescribed medicines, except sulfonylurea, decreased the HR of CVD. With the exception of chronic liver disease and cancer, COPD, hypertension, renal disease and a mental disorder elevated the HR of CVD.

Myocardial infarction, stroke and heart failure are major components of CVD. Table 3 shows that the rates of myocardial infarction and heart failure were decreased by advanced periodontal treatment, whereas the incidence of stroke was not altered. The HRs of myocardial infarction and heart failure were 0.92 (95% CI 0.85-0.99) and 0.60 (95% CI 0.45-0.80), respectively. The Kaplan-Meier curve showed that the incidence of CVD, myocardial infarction, and heart failure were significantly reduced in the advanced treatment-group (Fig. 2). In summary, advanced periodontal therapies reduce the incidence of some of the CVD events in diabetic patients.

Discussion

We herein demonstrate the cardiovascular outcomes of advanced periodontal treatment in patients with type 2 diabetes and periodontal problems. After propensity matching and adjustment for confounders, we demonstrated that the rates of myocardial infarction and heart failure were decreased by complete management. Our data show that sulphonylurea elevates the risk of CVD among patients with diabetes, which is consistent with a previous report (12). Furthermore, systemic disorders aggravate the occurrence of CVD, which is commonly observed during the clinical course. Although the present study investigated a retrospective cohort, we are of the opinion that these results are representative and conclusive since the NIH dataset covers almost all of the funda-

Table 2. Cox Proportional Hazard Model Analysis for the Occurrence of CVD.

	No. of patients	No. of CVD event	Crude HR	95% CI Lower	95% CI Upper	Adjusted HR	95% CI Lower	95% CI Upper
Advanced treatment								
No	12,156	6,420	1			1		
Yes	3,039	1,466	0.91 **	0.86	0.97	0.95	0.90	1.01
Age								
18-45	3,525	1,192	1			1		
45-64	9,321	4,939	1.88 **	1.76	2.00	1.85 **	1.74	1.98
≥65	2,349	1,755	3.75 **	3.48	4.04	3.12 **	2.89	3.37
Gender								
Female	6,085	3,190	1			1		
Male	9,110	4,696	0.98	0.93	1.02	1.00	0.95	1.04
Biguanides	7,293	3,248	0.60 **	0.58	0.63	0.69 **	0.65	0.74
Sulfonylurea	7,826	3,773	0.75 **	0.72	0.79	1.38 **	1.29	1.47
Alpha-glucosidase inhibitors	1,766	558	0.43 **	0.40	0.47	0.68 **	0.62	0.74
Thiazolidinediones	2,207	723	0.44 **	0.41	0.47	0.77 **	0.71	0.84
Glinides	1,050	380	0.55 **	0.49	0.61	0.84 **	0.76	0.93
DPP-4 inhibitors	840	55	0.08 **	0.06	0.11	0.13 **	0.10	0.17
Insulin and analogues	778	242	0.46 **	0.41	0.53	0.79 **	0.69	0.90
Statin	3,981	1,540	0.53 **	0.50	0.56	0.64 **	0.60	0.68
Hypertension	8,506	4,605	1.15 **	1.10	1.20	1.16 **	1.11	1.22
Chronic liver disease	3,032	1,522	0.96	0.91	1.02	0.98	0.92	1.04
COPD	1,233	777	1.46 **	1.36	1.57	1.18 **	1.10	1.27
Renal disease	516	308	1.29 **	1.16	1.45	1.15 *	1.03	1.29
Mental disorder	1,682	1,034	1.42 **	1.33	1.51	1.29 **	1.20	1.38
Cancer	487	268	1.29 **	1.14	1.46	0.99	0.88	1.12

*p<0.05, **p<0.01.

Table 3. Incidence of Myocardial Infarction, Stroke, and Heart Failure in Diabetes with Periodontal Treatment.

	observed person-years	No. of event	Incidence density (per 100 person-years)	Crude HR	95% CI Lower	95% CI Upper	Adjusted HR†	95% CI Lower	95% CI Upper
CVD									
Advanced treatment									
No	82,206	6,420	7.81	1			1		
Yes	20,250	1,466	7.24	0.91 **	0.86	0.97	0.95	0.90	1.01
MI									
Advanced treatment									
No	101,006	3,708	3.67	1			1		
Yes	24,537	815	3.32	0.89 **	0.83	0.96	0.92 *	0.85	0.99
Stroke									
Advanced treatment									
No	115,666	1,795	1.55	1			1		
Yes	27,376	385	1.41	0.91	0.82	1.02	0.95	0.85	1.06
Heart failure									
Advanced treatment									
No	122,732	397	0.32	1			1		
Yes	29,020	52	0.18	0.57 **	0.43	0.77	0.60 **	0.45	0.80

†Adjusted for age, gender, hypoglycemic agent, antihypertensive drug, statin and comorbidities.
*p<0.05, **p<0.01.

mental health records in Taiwan.

Periodontitis is a bacterially-induced, localized chronic inflammatory disease that destroys both the connective tissue and the supporting bone of the teeth. The etiology of periodontal disease is multifactorial, and is caused by interactions between micro-organisms, a host with some degree of susceptibility and environmental factors (13). According to the current scientific evidence, diabetes is itself a risk factor for periodontitis. The risk of periodontal disease in diabetic patients is 2-3 times that observed in healthy individuals, especially those with inadequate glycemic control as poor glycemic control results in poor immunity (13, 14). It has been shown that the advanced glycation end-products (AGE) can lead macrophages to produce high levels of interleukin-1beta (IL-1β) and tumor necrosis factor α (TNF-α) (15). These alterations can be used by bacteria to cause major periodontal damage (16). Nevertheless, periodontitis is also a chronic inflammatory source, and has reciprocal systemic impacts.

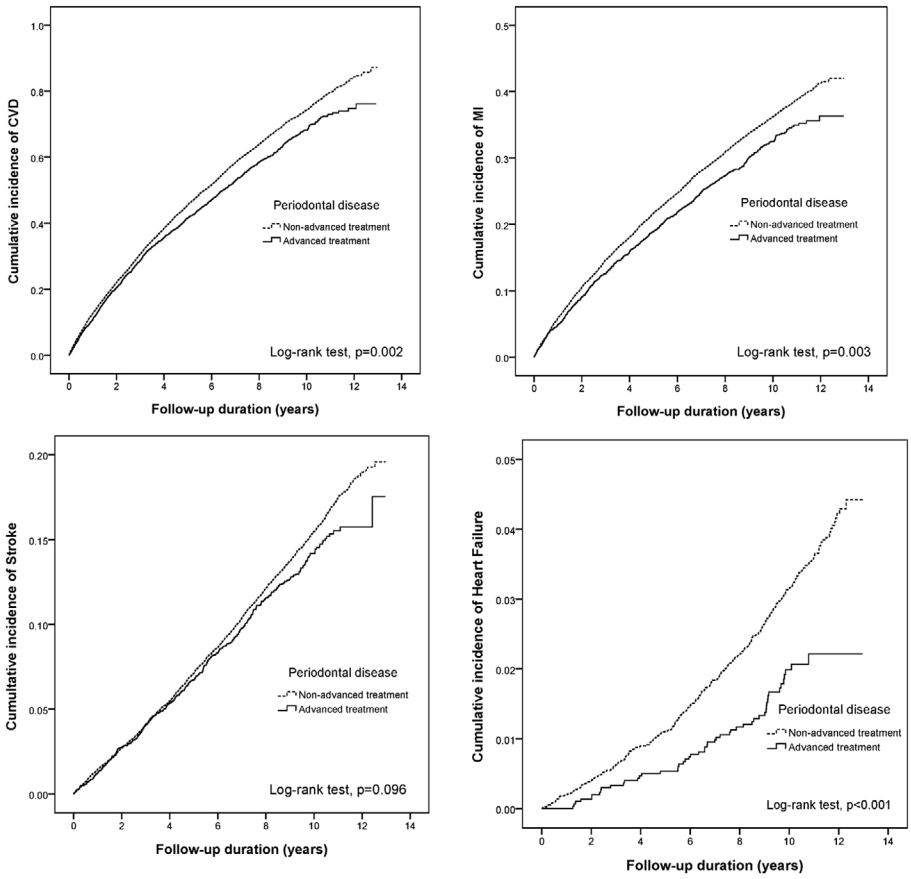

Figure 2. The Kaplan-Meier curves of the incidence of CVD, myocardial infarction (MI), stroke and heart failure.

Some reports have shown that hygiene and professional or domiciliary control can support the reduction of glycosylated hemoglobin (17). Relevant reductions in the levels of TNF-α and fibrinogen were observed after 3 months of non-surgical periodontal therapy (18). These molecular level findings may theoretically contribute to the reduction in diabetic complications among patients who receive periodontal treatment.

Inflammation is a critical pathogenic factor in atherogenesis. Ephemeral bacteremia, systemic inflammation and immune-pathological reactions constitute a triad of putative mechanisms that may lead to periodontal and cardiovascular damage (5). The resultant interplay among the endothelium, monocytes, and platelets might be proatherogenic (19-22), or adverse to the rupture of atheromatous plaque in subjects with periodontitis (19, 20, 23). Observational evidence suggests that the association between periodontitis and atherosclerotic disease is independent of known confounders (24). More recently, a large case-control study of periodontitis (Periodontitis and Its Relation to Coronary Artery Disease, PAROKRANK) by Rydén et al. (25) clearly demonstrated (after careful adjustment for confounding factors) that the risk of a first myocardial infarction was significantly increased in patients with periodontitis. These results enhance the evidence of an independent association between periodontitis and CAD. However, the extent to which each periodontitis-mediated component contributes to vascular damage still remains uncertain (5). Our analysis revealed that advanced periodontal treatment effectively alleviated the incidence of myocardial infarction and heart failure (the latter to a greater extent), whereas it had no significant effect on stroke. These results indicate there might be some discrepancies between the pathogenesis of stroke and periodontitis-associated CAD.

In the literature, although therapeutic intervention for periodontitis significantly decreased the C-reactive protein (CRP) level (26, 27), it was suggested that full-mouth mechanical debridement might induce a strong transient systemic inflammatory response in comparison to quadrant-wise mechanical debridement (28). Whether such an increase may lead to adverse effects remains unknown. In Taiwan's NHI program, periodontal treatment can be carried out locally or divided as one-third or half arch. Thorough debridement may reduce the transient risk and effectively prevent diabetic patients from suffering CVD morbidities.

The present study is associated with some limitations. First, it was not a randomized control trial study. However in real-world situations, it is difficult to conduct such a study due to potential ethical issues, as once a patient is diagnosed with periodontitis, it is unethical to treat them with a placebo. In reality, some diabetic patients with periodontal problems will not receive proper periodontal intervention for

personal reasons. We can take advantage of this fact to retrospectively compare type 2 diabetic patients with periodontal problems who received advanced treatment with those who did not. This happens to be one of the strengths of the present study, which used the Taiwan NHI dataset to provide evidence supporting advanced therapeutic intervention. Second, because the Taiwan NHI Research Database is primarily maintained for reimbursement, we could only obtain the periodontitis code and not the actual periodontal condition for comparison between the groups. Third, there was no health behavior record and a lack of data regarding the patients' characteristics, including their body mass index, smoking history and family history, due to the limitations of our database. As for the socioeconomic status, although a mild increase in the incidence of CVD was observed in relatively low-income areas and rural areas, after adjustment for the socioeconomic status, the advanced periodontal treatment still showed its effect on the rates of myocardial infarction and heart failure in the two groups of this cohort study (data not shown). However further investigation is needed to take all of these confounding factors into consideration.

In conclusion, periodontal therapeutic intervention may help to reduce the risk of cardiovascular complications in diabetes patients. Proper dental management should be suggested to improve the health conditions of patients with diabetes.

The authors state that they have no Conflict of Interest (COI).

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