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Exploration of the association between chronic periodontal disease and erectile dysfunction from a population-based view point

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Summary

Several cross-sectional studies have indicated an association between chronic periodontal disease (CPD) and cardiovascular disease and metabolic syndrome. Erectile dysfunction (ED) also shares pathological mechanisms with these diseases. Using a nationwide population-based data set, we examined the association between ED and CPD and assessed the effect of dental extraction (DE) on ED prevalence in different aged CPD populations in Taiwan. We identified 5105 patients with ED and randomly selected 10 210 patients as controls. Of these patients, 2617 (17.09%) were diagnosed with CPD according to the index data: 1196 (23.43%) in the ED group and 1421 (13.92%) in the control group. After adjusting for comorbid factors, patients with ED were more likely to have been diagnosed with prior CPD than controls (OR = 1.79, 95% CI = 1.64–1.96, $P < 0.001$). Moreover, the association was much stronger in the populations aged less than 30 years (OR = 2.13, 95% CI = 1.23–3.70, $P < 0.001$) and more than 59 years (OR = 2.27, 95% CI = 1.99–2.59, $P < 0.001$). Dental extraction seems to attenuate damage to the penile endothelial beds caused by CPD-related inflammation and overcame the process of ED in the middle-aged and older populations.

Introduction

Erectile dysfunction (ED) is the inability to attain and maintain an erection sufficient for satisfactory sexual performance. The development of ED is related to many risk factors, including age, smoking, diabetes, depression and hypertension (Johannes *et al.*, 2000). These risk factors are related to the impairment of endothelial function in cardiovascular disease, and it is this same mechanism that is thought to be involved in the development of ED (Montorsi *et al.*, 2009). An early case–control study indicated that subjects with chronic periodontal disease (CPD) had higher levels of endothelial dysfunction, measured as the flow-mediated dilatation of the brachial artery, compared with matched controls (Joshipura *et al.*, 2003). It is also been demonstrated that CPD impairs endothelium-dependent vasodilatation but not endothelium-independent vasodilatation in healthy young men (Dietrich *et al.*, 2008). Therefore, CPD is suggested to be a further risk factor for the development of ED, through penile endothelial dysfunction.

The relationship between CPD and ED is unclear; however, many hypotheses have been postulated. Tooth loss caused by CPD could affect chewing ability, leading to an altered diet, which could increase the risk of endothelial dysfunction. Alternatively, endothelial dysfunction could be a result of the increased inflammatory response associated with CPD (Joshipura *et al.*, 2003). CPD is a chronic inflammatory disease caused by colonising bacteria that affect the soft tissue and bone that support the teeth. High prevalence of CPD in the adult population is a serious public health problem, and periodontal disease is the principal reason for tooth extraction in patients over 40 years of age (Hung *et al.*, 2003; Reich & Hiller, 1993). Proper oral hygiene is necessary to successfully manage CPD. Treatment includes the removal of microbial plaques, and periodontal surgery may be needed if the condition is severe. Patients with CPD have been found to

have a 1.14 times higher risk of coronary heart disease than subjects without periodontitis (Meurman *et al.*, 2004). This was confirmed by a meta-analysis study (Bahekar *et al.*, 2007).

ED and CPD have been reported to have similar risk factors and associated systemic conditions related to the impairment of endothelial function. Recent studies have revealed a positive correlation between ED and CPD severity (Zadik *et al.*, 2009; Sharma *et al.*, 2011; Matsumoto *et al.*, 2014). These preliminary findings are consistent with theories that associate these conditions with systemic inflammation, atherosclerosis and endothelial dysfunction. Another study in a rat model showed that the total nitric oxide synthase activity and cyclic guanosine monophosphate (cGMP) level in cavernosal tissue were significantly lower in the periodontitis group than in the control group (Zuo *et al.*, 2011). No significant alteration was identified in the ultrastructure of the penile cavernosal tissue.

A study by Håheim *et al.* (2011) concluded that tooth extractions due to infections were associated with nonfatal myocardial infarction (MI) in elderly men and suggested that maintaining good oral health may be a necessary element for the prevention of MI. According to the conclusions of previous studies, the processes of MI and clinical ED development share common risks and disease pathways. A possible correlation between CPD and ED should be considered, and the effect of dental extraction (DE) on the attenuation of ED development should be investigated (Håheim *et al.*, 2011). Furthermore, an epidemiological study by Holmlund *et al.* (2006) concluded that the number of teeth is associated with the risk of MI, independent of age but not hypertension. This study supports the view that oral health is related to cardiovascular disease in a dose-dependent manner. Using a nationwide population-based data set, we examined the association between ED and CPD in different age groups and compared the prevalence of ED with the number of DEs in Taiwan.

Materials and methods

Database

The study population and matched controls for this case–control investigation were taken from the Longitudinal Health Insurance Database (LHID2000). The LHID2000 includes all the original claims data and registration files for 1 000 000 individuals randomly sampled from the 2000 Registry for Beneficiaries (n = 23.72 million) of the Taiwan National Health Insurance (NHI) programme. The Taiwan National Health Research Institute reported that there was no significant difference in the gender distribution between the sampled enrolees in the LHID2000 and the complete list of enrolees under the NHI programme. The LHID2000 permits researchers to follow up on all medical services rendered for these 1 000 000 individuals from the start of the NHI in 1996, and these data can therefore be utilised to better understand the association of CPD with ED. This study was exempted from review by the Taipei Medical University Institutional Review Board as it utilised the LHID2000, which consists of de-identified secondary data released to the public for research purposes.

Study sample

A matched case–control study of ED was conducted in Taiwan. Cases included ED patients ≥20 years of age and <80 years of age diagnosed with ED for the first time (International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM code 607.84) during visits to ambulatory care centres (including the outpatient departments of hospitals or clinics) between 1996 and 2008. We assigned the first ED diagnosis as the index date. To increase the validity of the ED diagnosis, we only included ED cases that consisted of at least two ED diagnoses, with at least one being made by a urologist. DE procedures (ICD-9-CM codes 23.0, 23.09 & 23.19) were traced prior to the ED diagnosis date. We then excluded patients under 20 years of age (n = 45). As a result, we enrolled 5105 cases with the date of their first ED diagnosis assigned as the index date. A total of 10 210 controls (two controls per case) were randomly selected and matched with cases in terms of age (<30, 30–39, 40–49, 50–59 and >59 years). We identified CPD cases based on ICD-9-CM code 523.4. To increase the validity of CPD diagnoses, we only included patients who had a consensus of at least two diagnoses of CPD prior to the index date.

To evaluate the causal relationship between the process of CPD and ED development, we compared the incidence of CPD and ED in different age groups and hypothesised that DE would extenuate endothelial damage. We also ensured that none of the selected controls had previously received any diagnosis of ED, regardless of whether it was psychogenic or organic, since the initiation of the NHI in 1996 until 2008. The regression model used was further adjusted for the incidence of hypertension (ICD-9-CM codes 401-405), ischaemic heart disease (IHD) (ICD-9-CM codes 410- 414), cerebrovascular disease (CVD) (430-437), diabetes mellitus (DM) (ICD-9-CM codes 250 & 648), hyperlipidaemia (ICD-9-CM codes 272.0-272.4) and obesity (ICD-9-CM codes 278.0 & 278.01). These co-morbidities have all been previously documented as being associated with ED and were therefore controlled for in this study. These co-morbidities were only included

if they were diagnosed prior to the index date. The SAS system (version 8.2; SAS Institute Inc., Cary, NC, USA) was used to analyse data, and $P < 0.05$ was considered statistically significant.

Results

In this study, a total of 15 315 samples subjects were enrolled with a mean age of 48.3 years (±12.5), including 5105 cases and 10 210 controls. Table 1 presents the demographic characteristics and co-morbidities of cases and controls. The cases had a higher prevalence of hypertension (47.56% versus 40.59%, $P < 0.001$), ischaemic heart disease (32.75% versus 22.79%, $P < 0.001$), cerebrovascular disease (20.45% versus 15.59%, $P < 0.001$), DM (32.24% versus 20.61%, $P < 0.001$), hyperlipidaemia (40.25% versus 25.81%, $P < 0.001$) and obesity (1.08% versus 0.52%, $P < 0.001$) than the controls.

The prevalence and odds ratios (ORs) of prior CPD between cases and controls are presented in Table 2. In total, 17.09% of the 15 315 sampled subjects had been diagnosed with CP prior to the index date. The prevalence of prior CPD was 23.43% and 13.92% for cases and controls respectively ($P < 0.001$). Similarly, the logistic regression analysis showed that cases were 1.79 times (95% CI = 1.64–1.96; $P < 0.001$) more likely to have been previously diagnosed with CPD than controls after adjusting for age, hypertension, ischaemic heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidaemia and obesity. Furthermore, compared with controls, the OR of previously having undergone DE within the 5 years preceding the index date was only 1.51 (95%

Table 1 Demographic characteristics of controls and patients with ED (n = 15 315)

	Patients with ED (n = 5105)		Controls (n = 10 210)		
variables	Number	%	Number	%	P -value
Age (years)					
<30	196	3.84	392	3.84	>0.999
30–39	575	11.26	1150	11.26	
40–49	1036	20.29	2072	20.29	
50–59	1278	25.03	2556	25.03	
>59	2020	39.57	4040	39.57	
Comorbid factors					
Hypertension	2438	47.56	4144	40.59	<0.0001
Ischaemic heart disease	1672	32.75	2327	22.79	<0.0001
Cerebrovascular disease	1044	20.45	1592	15.59	<0.0001
Diabetes mellitus	1646	32.24	2104	20.61	<0.0001
Hyperlipidaemia	2055	40.25	2635	25.81	<0.0001
Obesity	55	1.08	53	0.52	<0.0001

ED, erectile dysfunction.

Table 2 Prevalence and ORs of ED in patients with CPD and controls

	Patients with ED (n = 5105)		Controls (n = 10 210)		Total (n = 15 315)	
Variables	n; %		n; %		n; %	
CPD	1196	23.43	1421	13.92	2617	17.09
Adjusted OR (95% CI)	1.79* (1.64–1.96)		1.00			
CPD with DE	673	13.18	800	7.84	1473	9.62
Crude OR (95% CI)	1.56* (1.39–1.76)		1.00			
Adjusted OR (95% CI)	1.51* (1.34–1.70)		1.00			
CPD without DE	523	10.25	621	6.08	1144	7.47
Crude OR (95% CI)	2.22* (1.95–2.52)		1.00			
Adjusted OR (95% CI)	2.09* (1.84–2.38)		1.00			

Adjustments are made for age, hypertension, ischaemic heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidaemia and obesity.
ED, erectile dysfunction; CPD, chronic periodontal disease; OR, odds ratio.
*$P < 0.001$.

CI = 1.34–1.70) for cases. We also found that the adjusted OR of having been previously diagnosed with CPD after excluding those who had undergone DE was as high as 2.09 (95% CI = 1.84–2.38) for cases when compared to controls.

Table 3 shows the OR for prior CPD, stratified by age group. We found that ED was consistently associated with prior CPD in all age groups. In particular, case subjects aged >59 had the highest OR for prior CPD when compared to controls (OR = 2.27, 95% CI = 1.99–2.59; $P < 0.001$). In addition, among subjects aged <30, cases were 2.13 times (95% CI = 1.23–3.70; $P < 0.001$) more likely to have had been previously diagnosed with CPD than controls. The process of DE could attenuate the development of ED, except in younger age groups of <40 years old where the ORs for ED within patients with CPD receiving DE compared with controls showed no statistical difference (OR = 2.00, 95% CI = 0.91–4.40; OR = 1.29, 95% CI = 0.83–2.03; Table 3). Moreover, the ORs for the prevalence of ED among those with different times of DE was not significantly different compared with controls (data not shown).

Table 3 ORs of ED in patients with CPD, CPD patients with DE and controls, by age group

	Age group									
	<30		30–39		40–49		50–59		>59	
Variables	ED *n*; %	Controls *n*; %	ED *n*; %	Controls *n*; %	ED *n*; %	Controls *n*; %	ED *n*; %	Controls *n*; %	ED *n*; %	Controls *n*; %
CPD	29; 14.8	30; 7.65	96; 16.7	135; 11.74	184; 17.76	295; 14.24	307; 24.02	378; 14.79	580; 28.71	583; 14.43
Adjusted OR (95% CI)	2.13* (1.23–3.70)	1.0	1.42* (1.10–1.89)	1.0	1.31* (1.06–1.61)	1.0	1.76* (1.48–2.09)	1.0	2.27* (1.99–2.59)	1.0
CPD with DE	16; 8.16	13; 3.32	41; 7.13	60; 5.22	104; 10.04	144; 6.95	166; 12.99	215; 8.41	346; 17.13	638; 9.11
Crude OR (95% CI)	2.00 (0.92–4.36)	1.0	1.37 (0.89–2.12)	1.0	1.27(0.96–1.68)	1.0	1.45‡ (1.15–1.82)	1.0	1.77* (1.50–2.10)	1.0
Adjusted OR (95% CI)	2.00 (0.91–4.40)	1.0	1.29 (0.83–2.03)	1.0	1.35†(1.00–1.81)	1.0	1.40‡ (1.10–1.77)	1.0	1.74* (1.46–2.07)	1.0

Adjustments have been made for age, hypertension, ischaemic heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidaemia and obesity.
ED, erectile dysfunction; CPD, chronic periodontal disease; OR, odds ratio.
$^{*}P < 0.001$, $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$.

Discussion

The processes of MI and clinical ED development share common risks and disease pathways, and excellent oral health is necessary for the prevention of MI. In accordance with the study by Håheim *et al.* (2011), a possible correlation between CPD and ED should be considered, and the effect of DE on ED development investigated. Therefore, we applied for access to a population-based data set, the 'Longitudinal Health Insurance Database (LHID2000)', in Taiwan to analyse the relationship between CPD and ED.

To the best of our knowledge, this study is the first to focus on the relationship between CPD and ED, and to evaluate the attenuating effect of DE on ED development. We investigated the mechanism of this relationship by comparing the incidence of ED in patients with CPD receiving DE (OR = 1.51) and those who have not received DE (OR = 2.09). As the DE procedure involves the removal of inflamed tissue, the significantly lower OR for ED in patients with CPD receiving DE supports the theory that the association between CPD and ED proceeds through periodontitis-related inflammation.

The relationship between CPD and ED was more positively correlated in the younger population under 30 years of age. These results are in accordance with studies by Higashi *et al.* (2008) and Geismar *et al.* (2006), which showed that CPD is associated with the incidence of coronary heart disease (CHD) in younger men, independently of established cardiovascular risk factors.

According to Higashi *et al.* (2008), periodontitis at a younger age is a marker of higher disease susceptibility due to common pro-inflammatory factors, and this explains the continuous decrease in the CPD-ED association with increasing age (Higashi *et al.*, 2008). Geismar *et al.* (2006) explained that the association between periodontal disease and CHD is less pronounced in older populations due to a 'healthy survivor effect', where a selection may have taken place due to death from CHD. This modification of the effect of periodontitis by age is consistent with findings in studies of ischaemic stroke (Amar *et al.*, 2003; Grau *et al.*, 2004). The severity of CPD, therefore, plays a key independent role in ED development in younger populations due to an increase in pro-inflammatory susceptibility. However, the DE procedure revealed no significant attenuation of ED development in younger populations. This might be due to the majority of ED in younger populations stemming from psychological bases and may contribute to the stronger correlation between CPD and ED in young men in our study.

The other stronger association detected among the older age groups may be on account of long-term damage to their endothelium. Endothelial damage has been shown to be cumulative over the course of life (Ceriello *et al.*, 2002) and modulated by several lifestyle and biological factors with ageing (Seals *et al.*, 2011). Therefore, the CPD is not the only source of inflammation leading to damage to the vascular endothelium. Hence, the older population may be more vulnerable to the inflammation caused by CPD.

We assume that CPD is associated with ED just as it is associated with myocardial infarction, transient increased systemic inflammation and endothelial dysfunction. We believe that chronic inflammation with endothelium impairment links CPD and ED. Although the population-based study showed a significant association between CPD and ED, detailed laboratory study including investigation of endothelial function, cytokine levels and inflammatory markers is required to confirm the relationship.

The mechanism by which periodontitis might affect endothelial function remains uncertain. CPD has been linked with some chronic disorders such as endothelial dysfunction, and ED is thought to be an early sign of coronary heart disease (Billups, 2005). It has been inferred that systemic inflammation caused by periodontal pathogens might be the cause of endothelial dysfunction, and therefore, CPD might be associated with ED in the earlier life of men and later with coronary artery disease (Zadik *et al.*, 2009). Pihlstrom *et al.* (2005) highlighted that periodontitis involves bacterial infection by a range of gram-negative bacteria that invade superficial, and sometimes deeper, gingival tissues, depending on the severity of the condition. Therefore, these pathogens or their products could affect endothelial function directly, as simple actions such as brushing the teeth or chewing can result in ephemeral bacteraemia (Forner *et al.*, 2006). A recent study also suggested that poor oral hygiene is associated with ED (Oğuz *et al.*, 2013). Meanwhile, dental extraction also seems to extenuate the risk of bacteraemia, which activates the immune reaction. In cell cultures, *P. gingivalis* has been shown to invade endothelial cells (Haraszthy *et al.*, 2000), and periodontal pathogens have been identified in carotid atheromatous plaques in patients undergoing endarterectomy (Dorn *et al.*, 2000). Thus, these pathogens might act as a trigger for a systemic inflammatory response at the vascular wall. Therefore, DE in patients with CPD may eliminate or ease the inflammation of oral cavity and diminish systemic inflammation. The process can reduce bacterial seepage into the bloodstream and damage to blood vessels, which might prevent impaired blood flow and even maintain normal endothelial function in the penis.

Some limitations of this study should be addressed. The first is that the diagnosis of ED is only dependent on the use of ICD-9-CM coding in the National Health Insurance Research Database. The diagnosis of ED is not as objective as in other clinical studies, in which information on ED was collected using SHIM or IIEF-5 questionnaires rather than using the ICD-9-CM code. Second, the causes of dental extraction, such as periodontal infection or apical infection, caries and trauma, were not available. Third, the severity of periodontal disease could not be quantified using the population-based data.

Conclusions

This study utilised population-based data from the Taiwan LHID2000 to confirm a novel relationship between ED and prior CPD. It was also found that DE seems to attenuate ED development, except in the middle-aged younger population. CPD plays a key role in the pathological process of ED and is a risk factor that is independent of other morbidities and risk factors for ED. These findings will inform future studies on the association between chronic inflammation, endothelial dysfunction, periodontal disease and ED. Moreover, this work highlights a need for clinics dealing with patients with periodontal disease to assess erectile function.

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Conflict of interest

None.

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