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Association Between *Helicobacter pylori* Infection and Risk of Periodontal Diseases in Han Chinese: A Case-Control Study

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Background: This study was performed to test the association between *Helicobacter pylori* (HP) and periodontal disease (PD).

Material/Methods: This was a case-control study in a comprehensive hospital, including all patients with newly diagnosed PD between 2012 and 2014 as cases and all patients without PD as controls, thorough periodontal examinations. Those who tested positive for HP were examined by means of polymerase chain reaction. Single and multivariate logistic regression was used to analyze the data using SPSS 19.0 software.

Results: This case-control study included 212 Han Chinese non-smoking adults. The results indicated that HP-positive status significantly increased the risk of PD (2.63 times higher (odds ratio [OR]=2.63; 95% confidence interval [CI]=1.48–4.67). After adjustment for age, sex, level of education, physical exercise, body mass index, and history of alcohol and diabetes mellitus, this association remained significantly (OR=2.82, 95% CI=1.55–5.13).

Conclusions: PD might be associated with HP infection in adults and HP infection may be a significant and independent risk factor for PD.

MeSH Keywords: Case-Control Studies • *Helicobacter pylori* • Periodontal Diseases • Periodontitis

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Background

Periodontal disease (PD) is part of the global burden of disease (GBD) [1]. PD is possibly associated with 200 systemic diseases [2]. Published systematic reviews and meta-analyses indicate that PD is linked to many systemic diseases, such as pulmonary disease [3], cardiovascular disease [4], head and neck cancer [5], survival of dental implants [6], and diabetes [7]. Hence, seeking the risk factors for preventing PD is an important task. Besides the genetic factors [8–12], environmental factors also play a vital role in the development of PD [13]. Sex, cigarette smoking, alcohol, diabetes, obesity, metabolic syndrome, osteoporosis, dietary calcium, vitamin D, and stress are well accepted risk factors for PD [13].

Helicobacter pylori (HP) is cultured from gastric biopsy specimens of gastric inflammation and peptic ulcer patients and is considered to be responsible for these diseases [14], especially for gastric cancer worldwide [15]. Besides gastric diseases, published systematic reviews and meta-analyses demonstrated that HP is also associated with diabetes [16], chronic tonsillitis [17], atopic diseases [18], pancreatic cancer [19], recurrent aphthous stomatitis [20], myocardial infarction [21], and esophageal cancer [22].

Obviously, PD and HP are both associated with some diseases. HP is largely transmitted through oral-oral or fecal-oral routes and the oral cavity is a reservoir of pathogens [23], including HP [24]; HP is widely detected in the oral pathology [25]. Hence, there might be a link between HP and PD. The first relevant study was performed by Asikainen et al. [26] in 1994 and revealed a negative association; however, subsequent studies showed inconsistent results [25] and there is little data from Chinese populations. Therefore, this study was designed to investigate the association between HP and PD in Han Chinese.

Material and Methods

Study design and participants

We conducted a case-control study according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [27]. The patients were from the Department of Stomatology, Taihe Hospital, Hubei University of Medicine. All participants were enrolled between September 3, 2012 and September 2, 2014 and provided signed informed consent. All selected patients were nonsmokers. We excluded those who used prophylactic antibiotics or anti-inflammatory drugs, had a history of PD treatment, were receiving ongoing orthodontic therapy, had fewer than 6 teeth present, or had current pregnancy. This study was reviewed and approved by the Committee for Ethical Affairs of the Taihe Hospital, Hubei University of Medicine at Shiyan City, Hubei Province.

All potential eligible subjects were selected from Han Chinese population with similar age, sex, level of education, body mass index (BMI), physical exercise, history of alcohol use and diabetes mellitus, and other demographic characteristics. Two investigators were trained before the study and used standardized procedures to increase consistency. As controls we included all subjects with newly-diagnosed PD during the study period who met the same inclusion criteria as cases but did not have a diagnosis of PD. The diagnostic criteria was: PD was defined as presence of more than 4 teeth with 1 site or more having a probing pocket depth (PPD) ≥4 mm and clinical attachment level (CAL) ≥3 mm (24). These PPD and CAL were evaluated at 4 sites on each tooth (mesial, distal, buccal, and lingual) [28]. CAL was measured as the distance from the cemento-enamel junction (CEJ) to the base of the pocket.

Assessment of *Helicobacter pylori*

Subgingival dental plaques were collected from each case and control using a sterile universal curette. The dental plaques were broken and cultivated on Columbia agar plates (Oxoid of Thermo Fisher Scientific Inc., Waltham, MA, United States). The rapid urease test (RUT), a commercially available rapid gastric urease test kit, was used to for detecting HP, and the detailed methods of culture and polymerase chain reaction (PCR) are described elsewhere [24,29,30]. The sample was identified as positive HP if the test gel color changed from yellow to red within 20 min, up to a maximum of 60 min [24].

Statistical analysis

We used means with standard deviation (SD) or percentage to summarize the frequency distributions of age, sex, level of education, other demographic characteristics, and clinical characteristics of the study population. To investigate the association between HP and PD, the chi-square test or Fisher *Z* test was used to analyze the association, and the unadjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Considering the confounding risk factors of PD [31], we then performed a multiple logistic regression analysis to obtain adjusted ORs and their 95%CIs. We also performed subgroup analysis based on the above characteristics. A 2-sided $p \leq 0.05$ was considered statistically significant. All analyses were carried out using SPSS 19.0 software.

Results

A total of 212 participants with 103 cases and 109 controls were finally included (age range, 25 to 95 years). Tables 1 and 2 presents the relevant characteristics and prevalence of HP. Tables 1 and 2 shows that the basic characteristics of cases and controls were similar; however, the PPD, CAL, and number

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Table 1. Age, CAL and PPD level of participants.

Index	Cases	Controls	*P* value
Age (years; mean ±SD)	57.32±13.48	56.99±13.04	0.841
CAL (mm; mean ±SD)	4.46±0.75	2.55±0.55[a]	*P*<0.05
PPD (mm; mean ±SD)	5.11±0.81	2.98±0.64[a]	*P*<0.05

CAL – clinical attachment level; PPD – probing pocket depth.

Table 2. Characteristics of participants.

Index	Cases	Controls	*P* value
Gender (n)			0.168
Male	76	89	
Female	27	20	
BMI categories (kg/m^2; n)			0.400
Normal weight	48	50	
Overweight	47	55	
Obese	8	4	
Alcohol history (n)			0.487
None	96	104	
Yes	7	5	
Physical exercise (week)			0.111
None	57	50	
≥1 and <3 times	17	31	
≥3 times	29	28	
Level of education (n)			0.716
Less than university	40	45	
University or more	63	64	
History of diabetes mellitus (n)			0.669
None	98	105	
Yes	5	4	
RUT (n)			*P*<0.05
Positive *H. Pylori*	72	52	
Negative *H. Pylori*	31	57	
PCR (n)			*P*<0.05
Positive *H. Pylori*	78	58	
Negative *H. Pylori*	25	51	

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Table 3. Relationship of basic characteristics with PD occurrence based on multiple logistic regression model.

Index	OR	95% CI
Gender (n)		
Male	Reference [1.00]	
Female	5.07	0.35–73.10
BMI categories (kg/m^2; n)		
Normal weight	Reference [1.00]	
Overweight	0.19	0.004–9.32
Obese	1.69	0.85–33.64
Level of education (n)		
Less than university	Reference [1.00]	
University or more	0.57	0.41–8.06
History of diabetes mellitus (n)		
None	Reference [1.00]	
Yes	1.05	0.93–11.94
RUT (n)		
Negative *H. Pylori*	Reference [1.00]	
Positive *H. Pylori*	2.73	1.58–4.97
PCR (n)		
Negative *H. Pylori*	Reference [1.00]	
Positive *H. Pylori*	2.82	1.55–5.13

For the index of alcohol history and physical exercise, the value of ORs, lower CI or upper CI is too smaller or larger, so they were not showed in table.

of HP-positive individuals were significantly different between cases and controls.

In the unadjusted analysis, HP-positive subjects had significantly increased risk of PD (2.63 times higher) (95%CI=1.48–4.67) than HP-negative subjects. The estimates remained unaltered after adjustment for age, sex, level of education, physical exercise, body mass index, and history of alcohol and diabetes mellitus, and this association remained significant (OR=2.82, 95% CI=1.55–5.13) (Table 3).

Stratified analysis by sex, BMI categories, alcohol use history, physical exercise, level of education, and history diabetes mellitus indicated there were no significant interactions between PD and any of these exposure variables (Table 3).

Discussion

HP is a gram-negative, urease-producing bacterium that colonizes gastrointestinal mucosa and is considered as a risk factor for many oral diseases [25]. In this case-control study, we found that HP significantly increased risk of PD (2.82 times higher) after adjusting for age, sex, level of education, physical exercise, BMI, and history of alcohol use and diabetes mellitus. Our results differ from those of Asikainen et al. [26], published in 1994 and revealing a negative association; however, our results are similar to those of Dye et al. (OR=1.54, 95% CI=1.10, 2.16) [32]. Of course, there are many relevant published studies with inconsistent results [25] and we suggest a meta-analysis [33] on this topic, also for detecting the consistency of association [34].

The association between HP and risk of PD can be explained based on several mechanisms. In 2012 Bouziane et al. [35] carried out a systematic review and meta-analysis of randomized controlled trials, indicating that adjunction of periodontal treatment to eradication therapy appears to reduce gastric HP recurrence. First, there is experimental evidence that HP probably exists in the gingiva and plays a role in the development of PD. Second, this study included all non-smokers and the well-known risk factors of PD [31], such as alcohol use, diabetes, BMI, and physical exercise, were adjusted. After adjusting, the association remained significant and the risk was

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increased from 2.63 times to 2.82 times. For strength of association, the unadjusted OR is 2.63 and the adjusted OR is 2.82, which is a mild-to-moderate association. Third, gastrointestinal mucosa is the well-accepted place of HP colonization, and the oral mucosa is also a place for bacterial colonization, especially the gingival sulcus [31]. HP is largely transmitted through oral-oral or fecal-oral routes. Hence, we can conclude that the oral cavity is also a reservoir of HP.

Based on Hill's criteria [34], there are some limitations that should be addressed for further investigating the association besides the above items. First, our study is a case-control study and therefore it cannot reveal the temporal sequence of HP and PD. Whether PD exists first and then creates an environment for HP or whether HP plays a role in the onset and development of PD remains unknown. To address this question, we suggest a cohort study, especially a prospective cohort design. Second, the present study did not explore whether the severity of PD increases when the counts of HP are higher. Hence, relevant animal studies need to be carried out to determine if there is a dose-response relationship between HP and PD. Third, due to lacking the tissue of cases and controls, we could not to explore whether there is a genetic background. There are many increased risk polymorphisms of PD, such as interleukin-4 gene -590 C/T polymorphism [9], cyclooxygenase-2–1195G/A polymorphism [12], and interleukin-1α -899 (+4845) C/T polymorphism [36]. Hence, in further research, we suggest the investigators consider including the risk polymorphism in their study.

Our study can contribute to clinical practice. This is the first case-control study in a Han Chinese population who live in an upland city. Hence, it provides relevant evidence for similar populations. Second, this study provides some useful information for periodontists and gastroenterologists. Periodontists should ask patients about history of gastritis, gastric ulcer, and duodenal ulcer, especially for gastro-esophageal reflux disease (GERD) patients. If the patient has symptoms of these gastric diseases, the periodontist should suggest the relevant treatment in order to maintain the effect of periodontal therapy. Gastroenterologists also should pay attention to the history of PD of their patients. HP is easily transmitted into the stomach when drinking or eating. Hence, they should advise their patients to check and treat PD status during and after treatment for gastric disorders; this strategy might decrease the risk of gastric HP recurrence [35].

Conclusions

HP-positive patients had significantly increased risk of having PD compared with HP-negative subjects. Cohort studies would be valuable in demonstrating a temporal association between HP and PD. Hence, for better understanding the relationship between these 2 diseases, future cohort, especially prospective cohort studies, on immuno-inflammatory, usual risk factors, and genetic polymorphisms between the HP and PD are necessary. Periodontists and gastroenterologists should know about the potential association between HP and PD, and educate PD patients on the risk and the importance of their gastric disorders during dental visits and supragingival scaling.

Disclosure of conflict of interest

None.

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