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Review Article

Two-Way Relationship Between *Helicobacter Pylori* Infection and Periodontitis: Results from A Systematic Review and Meta-Analysis

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ABSTRACT

Aim: *Helicobacter pylori* (*H. pylori*) infection and periodontitis have considerable worldwide prevalence once they both present systemic alterations with a possible association between them. Therefore, we have performed this meta-analysis to assess the possible association between *H. pylori* infection and periodontitis.

Material and Methods: A systematic search in the literature was performed for studies published before December 2, 2019 in diverse scientific and educational databases. The data was extracted by two investigators and the statistical analysis was performed by Review Manager statistical program with heterogeneity and Odds Ratio (OR) with 95% of Confidence Intervals (CI) calculations as well as a sensitive analysis to assess the accuracy of the results. The value of $P < 0.05$ was considered as significant. In addition, we performed the analysis of the quality of included studies as well as the evaluation for risk of bias.

Results: In overall analysis, *H. pylori* infection was associated with the risk of periodontitis development (OR = 1.72, CI: 1.47, 2.02, $P < 0.00001$) and the periodontitis was considered as a risk factor for *H. pylori* infection (OR = 3.21, CI: 2.31, 4.47, $P < 0.00001$). Moreover, the evaluation of dental plaque from patients with periodontitis revealed increased risk of *H. pylori* infection (OR = 3.46, CI: 2.39, 5.01, $P < 0.00001$).

Conclusions: This current systematic review and meta-analysis composed by 12 studies in 7,059 participants showed that *H. pylori* infection increased significantly the risk of the development of periodontitis and the periodontitis may be a risk for this bacterial infection.

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Introduction

Helicobacter pylori (*H. pylori*) are gram-negative, spiral-shaped and microaerophilic microorganisms that colonize the human gastric-intestinal tract, specifically the stomach [1]. This bacteria species is commonly transmitted by oral-fecal way within family since early childhood with possibly persistence for decades in the gastric mucosa despite the host immune response [2]. This microorganism is already

associated with several gastric disorders from gastritis to gastric cancer [3, 4]. In the medical clinic scenario, several types of diagnostic methods are available to detect *H. pylori* infection, such as: histological evaluation, Rapid Urease Test (RUT), molecular techniques, serological kits and culture [5-7].

H. pylori infection also was associated with several others extra gastric conditions [8]. Studies available in literature report the relationship

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among *H. pylori* infection and heart failure hepatic insulin resistance pregnancy-related disorders and oral diseases [9-12]. Results from a meta-analysis showed a significant association between halitosis and *H. pylori* present in stomach with an Odds Ratio value of 4.03 [13].

In the field of oral diseases, there is the periodontitis, characterized as an immune-inflammatory disease as response to the presence of microorganisms in periodontal sites [14]. The pathogenesis of periodontitis receives influence of several factors including the colonization of periodontal sites by gram-positive and gram-negative bacteria species oral hygiene and genetic variations [15-19]. Both periodontitis and *H. pylori* infection had considerable worldwide prevalence and are associated with systemic conditions [8, 20-23].

In a recent case-control study, the possible association between *H. pylori* infection and risk of periodontitis was demonstrated which the *H. pylori* infection has represented an exposure influencing the outcome of periodontitis [24]. Indeed, others previous studies also have evaluated this association as well as have demonstrated the considerable prevalence of this microorganism in oral cavity [25-27]. However, other authors showed the inverse relationship, which the periodontal inflammation with the presence of *H. pylori* infection in periodontal pockets is indicated as source of the microorganism maintenance in human body and in the recurrence of gastric disorders even after an antibiotic therapy [25].

Up to the present moment, there has not been a study that gathered the results about *H. pylori* infection and periodontitis with an increased power of statistical association and which have demonstrated the real relationship between these two conditions. Given the lack of this information, this study aimed at performing a meta-analysis to assess the possible association between *H. pylori* infection and the risk of periodontitis based on case-control studies, observational studies or cross-sectional studies.

Material and Methods

This systematic review and meta-analysis is registered in PROSPERO database with the following ID number: CRD42017073192.

I Clinical Question Research

What are the real risk and association between *Helicobacter pylori* infection and periodontitis? May *Helicobacter pylori* infection be a risk for periodontitis or is periodontitis correlated with *Helicobacter pylori* infection?

II PICO Statement

The PICO statement used was the following [28]:

P – Patients, problem or population: Positive patients for *H. pylori* infection, patients diagnosed with periodontitis and healthy periodontal controls.

I – Intervention: Collection of the frequency of *H. pylori* infection between patients with periodontitis and control groups.

C – Comparison: The influence between the presence of *H. pylori* and periodontitis

O – Outcome: Odds Ratio calculation to measure the association between *H. pylori* infection and periodontitis and to assess the periodontitis as risk for *H. pylori* infection.

III Protocols Used

This meta-analysis followed the recommended PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [29]. The screened studies were evaluated by Newcastle-Ottawa scale for quality assessment studies with score < 7 were excluded [30]. This study (systematic review and meta-analysis) does not require approval by ethics committee.

IV Eligibility Criteria

Articles were included in the current meta-analysis if the studies met all the following criteria: 1) Evaluation of *Helicobacter pylori* infection with occurrence of periodontitis in humans; 2) Case patients received diagnosis of chronic, aggressive periodontitis or localized aggressive periodontitis and control patients had healthy periodontal evaluation; 3) Diagnosis of the periodontitis confirmed through clinical manifestations or radiographic findings as previously described and diagnosis of *Helicobacter pylori* infection confirmed by previous accurate methods and; 4) participants enrolled: analysis did not present pregnancy or previous systemic disorders such as diabetes or auto-immunity disease [5, 6, 31].

V Search Strategy

A comprehensive search in literature was performed by two investigators for studies that approached the association between *H. pylori* infection and periodontal disease. Google Scholar, MedLine, PubMed and Web of Science were the medical and scientific databases used in the literature retrieval. The following combined keywords or Medical Subject Headings (MeSH) were used: [(*Helicobacter pylori* or *H. pylori*)] and [(infection, gastric disorder)] and (periodontitis or periodontal disease or chronic periodontitis or aggressive periodontitis)]. There was no language restriction in the search strategy that approached studies published before December 2, 2019. The abstracts from included studies, as well as their references, were screened by investigators to identify potential additional studies.

VI Data Collection Process

Two investigators (FRPS and JGG) independently reviewed all studies and extracted the data using a standardized form. The data were collected on the first author, year of publication, study design, sample size, country, source of sample, method of detection of *H. pylori* infection and obtained score to assess the quality of included studies.

VII Statistical Analysis

The statistical analysis of the data was performed with the Review Manager software version 5.3 (RevMan, Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The chi-squared Q-based statistical test (I^2) was used to assess the presence of heterogeneity with evaluation of the Funnel plot for heterogeneity. When the value of I^2 was not

statistically significant ($I^2 < 50\%$, $P > 0.05$) the Fixed-effect model was used to estimate the pooled Odds Ratio (OR). On the other hand, when heterogeneity was significant ($I^2 > 50\%$, $P < 0.05$) the Random-effects model was used for the OR calculation. In both methods, the P value < 0.05 was considered statistically significant. In addition, a sensitivity analysis was also performed to test the robustness of the results pooled

by omitting one included study at a time to detect individual effects on the overall analyses and the risk of bias were assessed by use of the Cochrane Collaboration's tool [32]. All the data in the studies were dichotomous data expressed as OR with 95% of confidence intervals (CI) to assess the association between *H. pylori* infection and periodontitis.

Table 1: Characteristics of included studies in this systematic review and meta-analysis.

First author	Year	Sample size (Cc/Co)		Country	Source of sample	Method of detection	Subject type	Score
Al Asquah	2009	HP+	HP-	Saudi Arabia	Hospital	RUT	Dental plaque - Stomach	8
Anand	2006	37/13	25/26	India	Community	RUT and Serological test	-	9
Ding	2015	541/73	312/62	China	Hospital	HPS	-	8
Dye	2002	30/35	20/49	United States	Community	Serological test	Whites – Blacks – Mexican	9
Navabi	2010	189/951	463/3,981	Iran	Hospital	RUT	Men - Women	8
Nisha	2016	23/17	12/13	India	Community	RUT	-	8
Silva	2010	209/136	84/71	Brazil	Hospital	PCR	-	7
Souto	2008	12/1	50/30	Brazil	Community	PCR	-	9
Umeda	2003	39/4	130/52	Japan	Hospital	PCR	-	8
Yang	2016	7/1	10/10	China	Hospital	RUT, culture and PCR	-	8
Zheng and Zhou (1)	2015	50/20	24/46	China	Hospital	PCR	-	8
Zheng and Zhou (2)	2015	25/45	9/61	China	Hospital	PCR	-	8

Cc – Case patients for periodontitis, Co – Control patients, HP+ – *Helicobacter pylori*-positive patients, HP- – *Helicobacter pylori*-negative patients, RUT- Rapid Urease Test kit, HPS – saliva *Helicobacter pylori* antigen test, PCR – Polymerase Chain Reaction

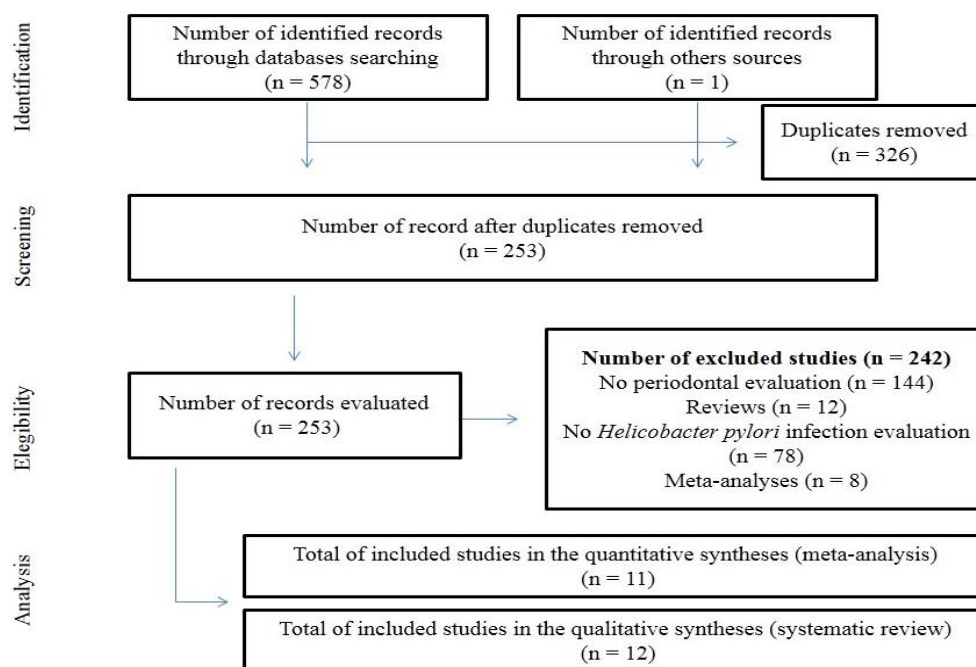


Figure 1: Flowchart for identification, screening, eligibility and analysis of included studies in this current meta-analysis.

Results

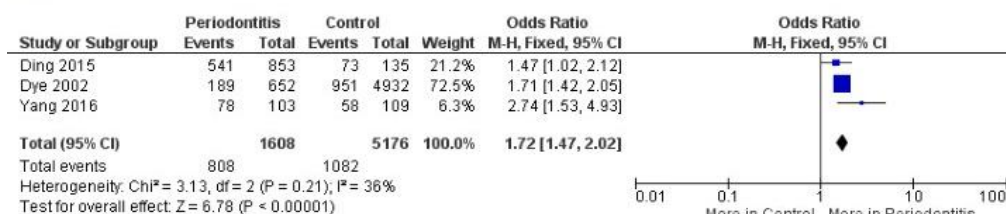
I Characteristics of Studies Included in the Systematic Review

The PRISMA checklist for this current systematic review and meta-analysis is available as supplementary material (Table S1). At the end of

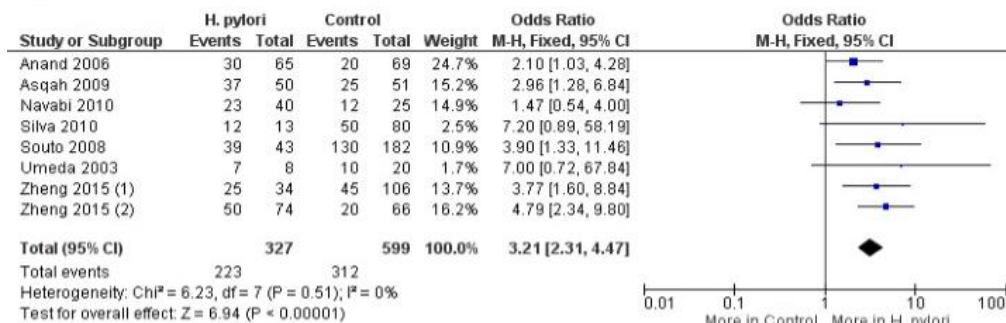
the systematic search, 11 articles [12, 25-26, 33-39] met the inclusion criteria and, therefore, composed the meta-analysis (Figure 1). One article stratified the results in two different PCR methods for *H. pylori* diagnosis. Seen this data, we considered that this article was composed by two studies. Therefore, this current systematic review brings 11 articles with 12 studies.

The studies were published between 2003 and 2016 and enrolled 7,059 participants. Diverse ethnical groups composed the studies and the patients were enrolled both in a Hospital-based population and a Community-based population [12, 24-26, 33-39]. The studies used four types of diagnosis methods for *H. pylori* detection: Rapid Urease test (RUT) Serological test to antibody against the bacteria Polymerase Chain Reaction (PCR) and saliva *H. pylori* antigen test (HPS) [12, 24, 25, 33-35, 37-39]. Three studies focused in to assess the *H. pylori* infection as potential risk factor for periodontitis [12, 24, 33]. On the other hand, eight studies were conducted to clarify the periodontitis as risk factor for *H. pylori* infection [25, 26, 34-39]. All studies presented more than seven points in the score scale and were included in the results. The Table 1 shows the main characteristics of the included studies.

A



B



C

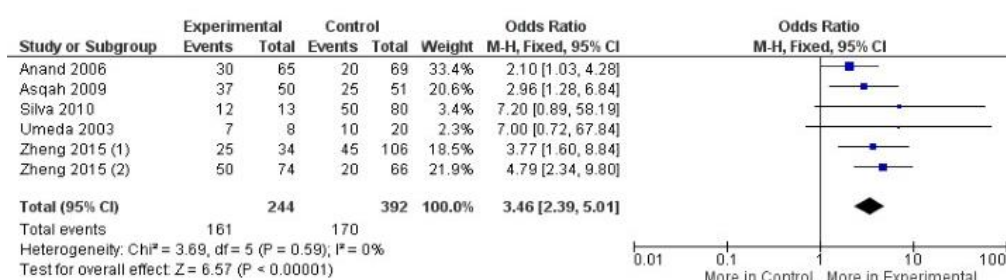


Figure 2: A) Forest plot to comparison between patients with periodontitis and control to *H. pylori* infection in overall analysis, B) Periodontitis as risk factor for *H. pylori* infection and C) Dental plaque from patients with periodontitis and *H. pylori* infection.

III Sensitive Analysis and Risk of Bias

The sensitive analysis showed that the study performed by Nisha et al. changed significantly the results in which considerable increase in heterogeneity was observed ($I^2 = 55\%$, $Pheterogeneity = 0.02$) [38]. When this study was excluded the heterogeneity has decreased to be unremarkable ($I^2 = 0\%$, $Pheterogeneity = 0.51$). Therefore, 11 studies have participated of the meta-analysis calculations. The risk of bias summary based in the Cochrane Collaboration's tool was showed in

II Meta-Analysis

The presence of *H. pylori* was associated with the risk of periodontitis development in overall analysis (OR = 1.72, CI: 1.47, 2.02, $P < 0.00001$) with non-significant value of heterogeneity ($I^2 = 36\%$, $P = 0.21$). Similar results were observed when periodontitis was evaluated as risk factor for *H. pylori* infection (OR = 3.21, CI: 2.31, 4.47, $P < 0.00001$) also with a non-significant value of heterogeneity ($I^2 = 0\%$, $P = 0.51$). The evaluation of dental plaque from patients with periodontitis revealed increased risk of *H. pylori* infection (OR = 3.46, CI: 2.39, 5.01, $P < 0.00001$) with decreased value of heterogeneity ($I^2 = 0\%$, $P = 0.59$). Due to the non-significant value of heterogeneity in the included calculations, the Fixed-effect statistical model was applied (Figure 2).

(Figure 3), in which all included studies failed to approach the several types of periodontitis classifications and, so, they presented elevated risk of others bias.

Discussion

To the best of our knowledge, this is the first meta-analysis to focus on the association between *H. pylori* and periodontitis as a two-way relationship. Some meta-analyses focused on determining the

association between *H. pylori* infection and extra gastric disorders such as: diabetes or halitosis [13, 40]. However, a specific two-way association between *H. pylori* infection and periodontitis by a complete meta-analysis has never been in the literature so far. Our meta-analysis showed that *H. pylori* might increase the risk of periodontitis development (Figure 2). *H. pylori* are a known microorganism that cause gastro-intestinal disturbances [3, 4]. The studies showed the capacity of *H. pylori* to promote stimulation to release interleukin-8 and a specific group of proteins associated with the periodontitis progression [41]. Although some authors suggested that this bacterial species might be in a commensal relation with the human body when present in the oral cavity, other subsequent study showed that *H. pylori* has an important role in oral disturbances [42, 43]. *H. pylori* may induce periodontal inflammation by the creation of antigen-antibody complexes who infiltrate in the gingival sulcus with periodontal inflammation [44].

On the other hand, the own periodontitis may be a risk factor for *H. pylori* infection (OR = 3.21, $P < 0.00001$). Results from a previous meta-analysis demonstrated that the periodontal therapy appears to reduce the gastric *H. pylori* recurrence [45]. Besides, other data available in the literature demonstrated that the dental plaque control was effective in preventing *H. pylori* to induce gastric disease [45, 46]. Despite these findings, *H. pylori* were detected more in supragingival plaque rather than in subgingival plaque, what may be signal that this bacterium species does not commonly colonize the periodontal pockets [37]. These authors are according with our results that demonstrated the increased risk of *H. pylori* infection in dental plaque from patients with periodontitis (Figure 2). The dental plaque is a biofilm that adheres to teeth as well as others surfaces in the oral cavity promoting an interesting advantage composed by the resistance to host immune response; Therefore, *H. pylori* as biofilm-associated is protected from host immune response and systemic antibiotics therapy [47].

Taken in base the evaluation by ethnicity, six studies performed the evaluation of *H. pylori* infection and periodontitis in Asian ethnicity, more specifically in India China and Japan and two studies were carried out among Brazilians [12, 24, 25, 34, 35, 37-39]. Anand et al. evaluated 134 subjects to assess the relationship between oral conditions and *H. pylori* infection. They detected 65 patients positive for *H. pylori* infection and 46.2% of these patients had periodontitis. *H. pylori* infection already had a significant prevalence in this population [48]. The high prevalence of *H. pylori* infection, as well as periodontitis, in populations from Asian and South America leads us to pay more attention in our results seen the limited number of included studies that have been performed in these aforementioned populations [20, 49].

This is the first meta-analysis focused on assessing the association between *H. pylori* infection and periodontitis, in which the results may be considered accurate by non-significant heterogeneity in the performed analyses. However, the meta-analysis has presented some important limitations that should be noted. First, 11 studies composed the results. Although a considerable number of patients was enrolled (Table 1), more studies are required to better evaluating the association between this bacterial infection and periodontitis. Second, *H. pylori* not only are present in patients that manifest gastric symptoms, but also in asymptomatic infected health patients [50]. Hence, the patients with periodontitis may be not diagnosed to *H. pylori* infection and therefore

are not included in the studies. Third, periodontitis itself has notable variations in clinical manifestations, diagnosis and therapeutic approaches; insufficient data brought by included studies did not enable a better evaluation due to such characteristics and may represent a potential bias as showed in (Figure 3). Fourth, two relationships have been approached in the included studies: whether the presence of *H. pylori* may influence in periodontitis, taken this disease as an outcome or whether periodontitis may be a cause of infection or reinfection by *H. pylori*.

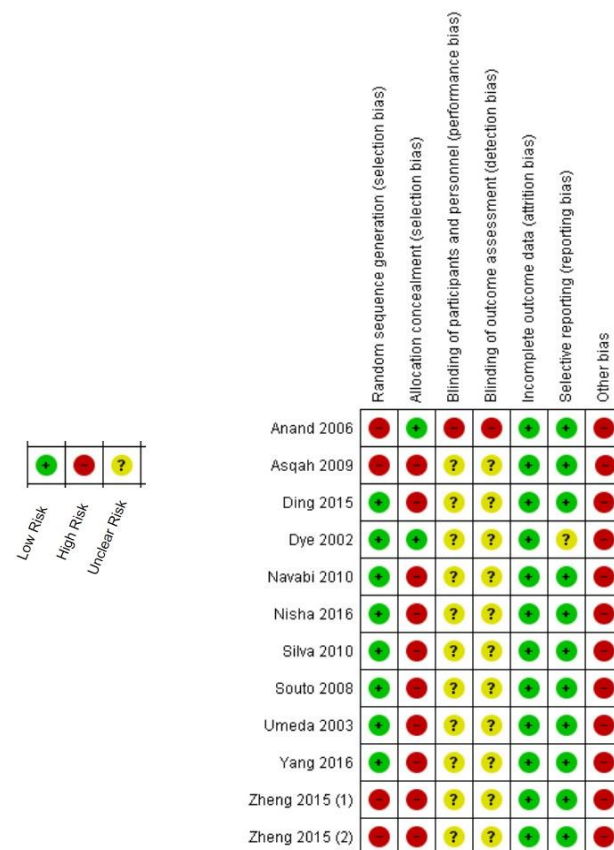


Figure 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

We tried to considerate this question. However, future studies should be focused on assessing the prevalence of *H. pylori* infection among patients with periodontitis and on the health periodontal evaluation assessing whether both groups present gastric alterations. Moreover, further researches should perform the evaluation of *H. pylori* infection as an exposure to periodontitis and the inverse evaluation. Fifth, periodontitis is a heterogeneous inflammatory condition that receives as environmental influence as host genetic conditions [15-19, 51, 52]. In conclusion, this current systematic review and meta-analysis composed by 12 studies in 7,059 participants showed that *H. pylori* infection is associated with periodontitis and the disease may be considered as a risk factor for *H. pylori* infection.

Conflicts of Interest

The authors declare there is any conflict of interest in this research.

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