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Review Article

Helicobacter pylori: Is there an Association with Oral Pathologies? A Traditional Review

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Abstract

Background: Given the works of Marshall and Warren, *Helicobacter pylori* found its place in scientific literature. Once evaluated the correlation between the microorganism and gastric pathologies, next studies are researching a possible role of *H. pylori* in the oral pathologies, since there is a direct continuity between oral cavity and stomach. Indeed, nowadays, it's possible to affirm that oral cavity represents the main extra-gastric reservoir of *H. pylori*.

Objectives: The purpose of this study is to analyze the relationship between *H. pylori* and important pathologies in the field of oral medicine.

Materials and Methods: This review takes in exam the articles published on PubMed in which the link between *H. pylori* and oral pathologies is analyzed. The pathologies appraised are: periodontitis, caries, neoplastic pathology, recurrent aphthous stomatitis, oral lichen planus, leukoplakia, peri-implantitis. Where possible, meta-analysis extracted from PubMed were considered.

Results: *H. pylori* is detectable in high numbers in mouth when dental plaque and poor oral hygiene conditions are present. This topographic association is related firstly to a higher risk of re-infection and, secondly, it can imply a causal connection which could assume a remarkable plausibility within the infectious oral pathologies.

Conclusions: Current data show a possible correlation between *H. pylori* infection and periodontitis, caries, recurrent aphthous stomatitis, oral lichen planus and leukoplakia. It seems, however, there is no positive correlation between oral squamous cell carcinoma and the microorganism. Regarding peri-implantitis, the bacterial strain-typing only demonstrates the presence of *H. pylori* in peri-implantitis sites without studying a potential causal link.

Keywords: Helicobacter pylori; Oral Pathologies

Introduction

Helicobacter pylori (*H. pylori*) is one of the bacteria that mainly causes infections in humans. The global prevalence of infection amounts to more than 50% [1]. We can observe that the prevalence of infection is epidemiologically higher in developing countries and in the lowest social classes, and that its seropositivity increases with age [2].

H. pylori infects not only human beings but also some species (*H. heilmanii* and *H. felis*) infect dogs [3] and cats [4]. *H. pylori* routes of transmission are oral-oral, fecal-oral and iatrogenic. *H. pylori* is a Gram-negative, micro-aerobic and its presence is strictly related to several gastrointestinal pathologies such as chronic gastritis, peptic ulcer and atrophic gastritis. Nevertheless, recent data suggest a possible association with other conditions like anemia [5], altered serum levels of lipoproteins [6] and oral pathologies that are the focus of our review.

In fact, there is a close relation between *H. pylori* infection in the stomach and the oral cavity: the mouth can be considered the main extra-gastric reservoir [7]. In particular dental plaque represents the main extra- gastric reservoir and it can be implied in

the treatment of *H. pylori* infection. The management of the infection needs antibiotics and other drugs. Despite the effectiveness of treatments for gastric eradication, the re-infection risk is high enough [8]. Some researchers sustain that the oral cavity, since reservoir of H. pylori, plays an important role for what concerns the post- eradication re-infection [9].

Presence of *H. pylori* in the stomach

The *H. pylori* colonization in the stomach occurs when the microorganism overcomes the acid mucus barrier. The bacterium is able to increase the pH of the environment through the urease enzyme which hydrolyses urea, and by its motile ability penetrates the mucus layer to reach a comfortable niche between the epithelial cells and the mucus in order to survive. Once here, *H. pylori* binds to gastric epithelial cells in several ways, for example through BabA and lectins (membrane proteins). The bacterial virulence is related to virulence factors CagA and VacA, which are involved in cell polarity alterations [10].

Gastric cancer is one of the main cause of death for cancer in the world. According to IARC, it was listed 4th in 2008 [11]. The 74% of non-cardia gastric cancer is attributable to *H. pylori* with relative risk (RR) of 5.9 [12]. The most common risk factor of gastric cancer is indeed *H. pylori* but some other risk factors were defined such as smoking, hyperglycemia, salt and red met [10]. It was noted that there are some benefits conferred by *H. pylori* infection. Some data suggest an inverse relation between *H. pylori* and asthma and allergy [13]. Seropositivity in children seems to be inversely related to allergic rhinitis, eczema and rash [14]. The connection between gastric pathology and the presence of the bacterium in the oral cavity is supported by the results obtained by Krajden., *et al*. [15] isolating *H. pylori* in culture from patients affected by gastric pathologies. They evidenced that at least one strain of the *H. pylori* isolated from dental plaque was strictly genetically linked or identical to the one isolated from stomach.

Presence of *Helicobacter pylori* in oral cavity

Some authors suggest that *H. pylori* belongs to the normal flora of oral cavity in very low numbers keeping a commensal interaction with the host [16,17]. Zou., *et al*. [18] underlined that oral cavity can be a source of re- infection after the gastric eradication, given that oral cavity is an important reservoir of *H. pylori*. They also observed that the eradication is more difficult in oral cavity rather than in the stomach.

The prevalence of *H. pylori* in dental plaque was studied by several investigators, and it ranged from 0% to 100%. This wide variation may be explained by several factors, such as characteristic of the sample populations, differing sampling procedures and differing methodologies used to detect the microorganism in dental plaque [19]. The reason why the eradication of *H. pylori* from the stomach doesn't mean eradication from the oral cavity is still linked to the fact that *H. pylori* is a bacterium able to form biofilm structure in the oral cavity, where bacteria are strictly joined each other and so protected from the external attack by the extracellular matrix. It involves a great resistance to antibiotics and, in general, antibacterial agents. About saliva, the prevalence of *H. pylori* is instead lower than plaque and only few studies reports a prevalence higher than 50% [19]. The reason why the prevalence of *H. pylori* in saliva is low could be related to the oral biofilm. In effect *H. pylori* is part of a stable biofilm in the oral plaque, stably adhering to hard dental surfaces, while it cannot occur in saliva.

Some authors such as Bali., *et al.* [20] have noticed a correlation between poor oral hygiene and gastric infection by H. pylori.

Helicobacter pylori and periodontitis

Periodontitis is one of the most prevalent disease and it influences up to 90% people in the world [21]. Differently from others infectious pathologies, periodontitis is linked to the presence of several bacterial species and in particular three strong- associated pathogens and eight moderate-associated pathogens, including *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella forsythus, Prevotella intermedia*. Subgingival plaque is responsible for the development of the periodontal disease: poor oral hygiene has been observed promoting the presence of *H. pylor*i in dental plaque [22-24]. It was also noticed that people infected by *H. pylor*i tend to contract the disease. Zhu., *et al.* [25] have observed how the presence of H. pylori in the stomach could be pathogenically involved in chronic periodontal disease.

The majority of the studies which wanted to highlight a relationship between *H. pylori* and periodontal disease have considered clinical index; only few of them evaluated the molecular expression of inflammatory proteins in the periodontal disease (the expression of the Wingless proteins is involved in the periodontitis [26]). In 1994 Asikainen., *et al.* [27] conducted in Finland the first research of H. pylori in subgingival plaque. Them put in evidence through PCR technique the absence of the bacterium in patients with periodontal disease. It wasn't detected the presence of *H. py-*

lori in any of 336 patients affected by periodontal disease included in the study. However, in 1999, Riggio., *et al.* [9], found out the presence of *H. pylori* in the 38% of the cases by using PCR too. This study suggest that subgingival plaque is a reservoir of *H. pylori* and so it could be related to the re-infection after gastric eradication. Zheng e Zhou [28] considered gastric *H. pylori* infection as a risk factor in the development of periodontal disease and so they concluded that gastric pathologies caused by *H. pylori* and the incidence of periodontal disease are linked.

Silva., *et al*. [29] observed this association too. Dye., *et al*. [30] tried to detect a correlation between probing depth and the *H. pylori* infection. They noted that compromised periodontal conditions (periodontal pockets > 5 mm in depth) is accompanied by a greater probability of seropositivity for *H. pylori*. Zhekay., *et al.* [31] evaluated the connection between the *H. pylori* infection and periodontal disease, observing that patients with and without *H. pylori* infection do not present differences in terms of plaque index and bleeding index while patients with *H. pylori* show higher depth probing and more attachment loss compared to those without infection.

Other studies investigated the positive linkage between oral hygiene conditions (and therefore the amount of dental plaque) and the presence of the microorganism both at the gastric and oral level [32,33]. Once understood that: 1) oral cavity represents the main extra-gastric reservoir of *H. pylori*; 2) poor oral hygiene is correlated to gastric infection and re- infection; 3) the gastric eradication therapy (even if successful) has a limited effect of on the oral H. pylori [34,35], it seems clear that the eradication therapy should be associated with control interventions of the oral plaque, as concluded by Pradeep., *et al* [19].

The results obtained by studies, which assessed the effectiveness of the gastric eradication therapy coupled to the periodontal therapy, have been analyzed by two systematic reviews of 2012 and 2016 [36,37]. They concluded that the periodontal therapy increases the effectiveness of the gastric eradication therapy and, at the same time, the risk of re-infection decreases. Both reviews underline a lack of data quality and quantity.

Helicobacter pylori and caries

Dental caries is a progressive chronic disease characterized by a multifactorial etiology, in which bacteria are the primary cause. The illness caries should be distinguished from the sign of caries. The former represents an imbalance of the normal bacterial biofilm, the latter is destructive process of demineralization of hard tooth tissues, which comes from the caries disease itself. In 2013 Liu., *et al*. [38] examined a sample of 841 patients: they found that 574 patients were positive for the *H. pylori* infection and they presented caries in the 73.52% of the cases. Instead, among the 267 patients whom were negative for *H. pylori* infection, the prevalence of caries was of 35.21%. Therefore, the authors concluded that there is a positive relationship between *H. pylori* infection and the prevalence of caries.

Streptococcus mutans (*S. mutans*) and *Streptococcus sanguinis* (*S. sanguinis*) are the main members of oral biofilm. However, *H. pylori* can be detected in dental plaque too, having an important role in its development. Zang., *et al.* [39] in 2018, wanted to evaluate the effect of *H. pylori* culture supernatant on *S. mutans* and *S. sanguinis* dual species biofilm and to evaluate also its potential ability on affecting dental health. They observed that *H. pylori* supernatant is able to inhibit the composition of *S. mutans* and *S. sanguinis* biofilm. Nevertheless, the inhibition of *S. sanguinis* is significantly greater than *S. mutans* one. It causes an alteration of biofilm in favor of *S. mutans*, which becomes the dominant bacteria, promoting caries development. In this study the assessment of genic expression suggests that *H. pylori* supernatant can induce the production mutacins (bacteriocins produced from *S. mutans*) and enhance its acidogenicity, making a convenient environment for *S. mutans* itself.

Urban., *et al.* [40] in 2017 pointed out that *H. pylori* is able to interact with the oral ecosystem: *S. mutans*, the first colonizing cariogenic bacterium, finds its ideal conditions of colonization when *H. pylori* is present in low numbers. They also noticed that *H. pylori* DNA was found in the oral cavity of 46% of patients that were positive for urease test due to the presence of *H. pylori* at the gastric level, and *H. pylori* virulent strains were found in 16% of these. Than it was found, with statistical significance, that *S. mutans* levels were higher in patients without *H. pylori* infection. The prevalence of *H. pylori* in the oral cavity among patients with gastric *H. pylori* seen by Urban., *et al.* is comparable to what observed by Gebara., *et al.* in which the 43% of 100 patients with *H. pylori* at the gastric level, showed *H. pylori* in the oral cavity [41]. At the same way, Gebara., *et al.* found an association between the poor oral hygiene (predisposing factor for caries) and the presence of *H. pylori* in high numbers in the oral cavity: we understand the importance of oral hygiene as an important in order to promote the eradication of *H. pylori*.

About Lactobacillus, associated with the evolution of the carious processes, more colonies were observed in patients with oral *H. pylori* compared to patients without oral *H. pylori*, but the difference is not statistically significant [40].

A Finnish retrospective study evidenced an association between infantile *H. pylori* infection and the risk of developing caries in childhood [42].

Helicobacter pylori and neoplastic pathology

Only a few studies have investigated the correlation between *H. pylori* infection and oral cancer.

Adler., *et al*. [7] did not find this correlation in patients with oral squamous cell carcinoma (OSCC). They used various methods as diagnostic techniques, and each method reported the same results. Despite the narrow sample (8 dyspeptic patients with OSCC), the results of Adler., *et al*. are aligned with those of other studies, including that of Grandis., *et al*. [43], in which differences of seroprevalence between control group of 21 patients and study group of 21 patients too, were not statistically significant. Fernando., *et al*. [44] also evidenced that there are no differences between study and control groups, but they found a statistically significant difference between non-betel chewers and betel chewers, in whom *H. pylori* was present in highest numbers. So, the authors concluded that betel could facilitate the colonization of *H. pylori* in the digestive tract.

Meng., *et al*. [45] explored the connection between *H. pylori* infection and the OSCC too: they suggested that *H. pylori* infection may be negatively related to the OSCC. A reverse association of *H. pylori* infection with the OSCC risk in the subpopulation with age ≥ 60 years was also found.

Helicobacter pylori and recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) also called recurring oral aphthae is a condition characterized by erosions, ulcers, necrotic ulcers and erythematous areas. We can distinguish three different types of aphthous stomatitis: minor, major and herpetiform. The etiopathogenesis remains still unknown. However, it seems that canker sores present an immune pattern associated with blood disorders, hormonal disorders, gastric disorders and local traumas [46].

Regarding the role of *H. pylori*, Porter., *et al.* [47] in 1997 wanted to compare the serological presence of IgG anti-*H. pylori* in patients with RAE versus patients with other ulcerative oral diseases or with healthy controls. They asserted that there is no significant difference between seropositivity in these three groups.

Tas., *et al*. [48] in 2012 evaluated the impact of *H. pylori* eradication on the clinical course of RAE. 46 patients joined the study. B12 levels and numbers of aphthous lesions were registered for each patient. Of these 46 patients, 30 were positive for *H. pylori* in the stomach. The latter received an eradication therapy: in 18 patients occurs a successful eradication, contrary to the other 12. Six months after eradication, vitamin B12 levels and the number of aphthous lesions were evaluated. Vitamin B12 levels were observed to be increased in patients in whom significant eradication occurred and the number of aphthous lesions also decreased in significance way. They concluded that there might be a benefit in the eradication of *H. pylori* in patients with recurrent aphthous stomatitis. The mechanism could be related to the increase of vitamin B12 after the eradication.

Given conflicting data in individual studies, we report a meta-analysis conducted by Li., *et al*. [49] in 2013 in which several studies were included. From the obtained results, the authors concluded that there is an association between HP infection and an increased risk of development of RAS.

Helicobacter pylori and lichen planus and leucoplachia

Oral lichen planus is a chronic inflammatory T-cell mediated disease of the oral mucosa. Its etiology is not entirely clear, despite the hypotheses that antigen- specific mechanisms and non-specific mechanisms are involved [50,51].

Leukoplakia is a potentially malignant lesion. We can identify two forms: an idiopathic one and the other one associated with tobacco use. From a histological point of view there may be variations of presentation: orthocheratosis, parakeratosis, hyperkeratosis, inflammatory infiltrates of the lamina propria. Sometimes various levels of dysplasia can be found in the minority of lesions [52].

The study by Kazanowska-Dygala., *et al*. [53] wanted to evaluate the presence of *H. pylori* DNA in the oral cavity of patients with leukoplakia and oral lichen planus, assuming that many studies define the oral cavity as an important extra-gastric reservoir of *H.*

pylori. Their study included 54 patients with leukoplakia, 72 with oral lichen planus and 40 healthy controls. The presence of *H. pylori* in the oral cavity was detected by the PCR method. It was observed that 20% of patients with leukoplakia and 23% of patients with lichen had *H. pylori* DNA. Healthy controls had no *H. pylori* DNA in the mouth. These results suggest that the presence of *H. pylori* in the oral cavity may therefore be related both to leukoplakia and lichen planus lesions.

H. pylori exists at pharyngeal level too, and it is related to leukoplakia of the vocal folds. Chen., *et al.* [54] indicated the larynx as possible *H. pylori* reservoirs. Their study explored the association between *H. pylori* and vocal fold leukoplakia: *H. pylori* infection exists still in the larynx and may be associated with vocal fold leukoplakia.

Helicobacter pylori and peri-implantitis

Peri-implantitis is an inflammatory process which involves tissues around the osseointegrated implant, leading to the loss of supporting bone tissue. Peri-implantitis recognizes an infectious and traumatic etiology which are not clinically mutually exclusive.

By typing in Pubmed '*Helicobacter Pylori* peri-implantitis' the research returns two articles. The most recent one, by Persson., *et al.* [55] of 2013, wanted to typify the bacterial species mainly associated with peri-implantitis sites. 166 patients with peri-implantitis were included in the study and the results were compared to those obtained from 'healthy' implants in 47 individuals. The microbiological counts showed that among the 19 species detected in greater quantity in the peri-implantitis sites *H. pylori* was present.

Another study, also by Persson [36], in 2010, evaluated the bacterial count before and during the 6 months following the mechanical treatment of peri-implantitis (using curettes and an ultrasonic device). Once again, among the most present species appears *H. pylori*. In general, there were no differences in terms of reducing the microbiota in peri-implantitis by mechanical treatment.

Conclusion

The majority of the studies examined in this review are in agreement about considering the presence of *H. pylori* in dental plaque as a risk factor for re-infection in gastric pathology. Since the microorganism inhabits the dental plaque depending on the state of hygiene (as described by many authors) the eradication protocol of *H. pylori* at the gastric level should include maneuvers and interventions for oral sanitation in order to reduce the possibilities of re-infection and to promote complete eradication.

Periodontitis: The positive correlation between *H. pylori* and periodontitis has been recorded in several studies, of which only a few of them have considered the molecular aspects of this association [31]. The relationship between gastric pathology from *H. pylori* and periodontitis is supported by the fact that periodontal therapy when associated with gastric eradication therapy increases its efficacy also in the long term, reducing the risk of infection, as evidenced by two systematic reviews.

Caries: A positive relationship with *H. pylori* infection has also been detected for caries. However, the presence of *H. pylori* inhibits in vitro the development of S. mutans and also this positive correlation in dental plaque has been recorded *in vivo* with statistical significance. However, studies have shown that despite the inhibition of *H. pylori* on *S. mutans in vitro*, the former induces changes in the microenvironment that would increase the pathogenicity of the latter. Still *in vivo* but without statistical significance, one study found a greater presence of Lactobacillus (associated with carious progression) in presence of *H. pylori.*

Oral Cancer: The correlation with gastric carcinoma and *H. pylori* has been extensively described in the literature, differently from the oral squamous cell carcinoma.

From the available data, a direct correlation between squamous carcinoma of the oral cavity and *H. pylori* has not been described. On the contrary, a study showed an inverse correlation. It was differently observed that a greater presence of *H. pylori* was found in betel chewers (risk factor for OCSC).

Recurrent Aphthous Stomatitis: The results of the studies examined are conflicting. We have therefore examined a systematic review in which a possible positive correlation is highlighted.

Leukoplakia and Oral Lichen: Given the results of the studies considered in this review, the development of these lesions could be related to the presence of *H. pylori*.

Peri-implantitis: In this regard, only two studies are indexed on PubMed: none of these has tried to identify a causal association between *H. pylori* and the development of peri-implantitis. Therefore, only the topographic association was found but actual knowledge on microbiota in peri-implantitis is still limited.

Given the poor quality and quantity of studies and conflicting results in individual articles in some cases, it would be necessary to carry out other well-designed studies, in order to confirm (or not) the present results.

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