PERIODONTAL POCKETS AS A RESERVOIR OF *HELICOBACTER PYLORI* CAUSING RELAPSE OF GASTRIC ULCER: A REVIEW OF THE LITERATURE

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***Helicobacter pylori* (HP) is one of the most common gastric infections in the world, affecting about half the world's population, and is the principal cause of adenocarcinoma of the distal stomach. It seems that HP infects the subject early in life and is transmitted from person to person. The HP reaches the stomach through oral ingestion, and because of its non-invasive nature, the stomach is the ultimate site of colonization. Recently, it has been debated whether the oral cavity is a reservoir of HP bacteria participating in infection transmission, or representing a nidus of re-infection after eradication of the bacterium. HP and recurrent aphthous stomatitis (RAS) show similar clinical and histological findings, and the discovery of HP in RAS ulcers support the idea of a correlation between the two diseases. Another important relationship between RAS and HP is the high incidence of anemia in patients with RAS that may be caused by HP-positive stomach disease. In fact, antibiotic therapy and treatment of anemia can reduce the frequency of RAS ulcer recurrence. HP is considered a carcinogenic agent type 1 of the stomach by the International Agency for Research on Cancer. In conclusion, the oral cavity is an extra-gastric reservoir of HP and periodontal therapy associated with systemic therapy can better eradicate HP from the mucosa of all gastro-enteric tract, reducing relapse of HP infection. Prospective cohort studies are needed to demonstrate the bacterial action in the oral cavity.**

Helicobacter pylori (HP) is one of the most common gastric infections in the world, affecting about half the world's population and is the principal cause of adenocarcinoma of the distal stomach (1). The risk of developing gastric cancer is related to the different subtypes of HP and to the inflammatory response mediated by genetic factors (1).

HP presents two different microbiological forms, spiral and coccoid. The spiral form is virulent, whilst the coccoid form may be a dead form of HP, and its role in transmission of infection is not clear (1).

It seems that HP infects the subject early in life and is transmitted from person to person (2). The transmission of the bacterium is related to crowded living associated with low socio-economic conditions and intra-familial clustering. However, the exact manner of transmission is not yet known (3). HP reaches the stomach through oral ingestion, and because of its non-invasive nature, the stomach is the ultimate site of colonization (3). The evidence

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of oral transmission includes the high prevalence of HP in African children who are fed with food pre-masticated by the mother (4), and in populations that exchange chopsticks (5).

In our study, we review the relationship between oral disease and HP and the role of the oral cavity as an extra-gastric reservoir of HP.

Periodontal disease and HP

Periodontal tissues include four defined structures that constitute the support of teeth: gingiva, cementum, alveolar bone, and the periodontal ligament. Periodontal diseases are extremely prevalent worldwide, affecting roughly half of the adult population. Its prevalence is similar to HP diffusion in the world population. Gingivitis, the mildest form of periodontal disease, is a rapidly inducible and reversible inflammatory affection of gingiva, mainly caused by accumulation of bacterial biofilm. The combination of bacterial infection and persistent inflammatory response can eventually induce the progressive destruction of the deeper periodontal tissues, a worse form of periodontal disease called periodontitis. Additional risk factors include genetic susceptibility, tobacco smoke, alcohol intake, and systemic conditions such as diabetes, osteoporosis, malnutrition and stress. Effective treatment of periodontal infections is important to reduce local inflammation and bacteremias. In addition, poor periodontal health appears to increase the risk of HP-induced gastric diseases.

The presence of HP in the oral cavity was discovered for the first time in 1989 when the bacterium was cultured from dental plaque of a patient with gastritis associated with HP infection (6).

Recently, it has been debated whether the oral cavity is a reservoir of HP bacteria participating in infection transmission, or representing a nidus of re-infection after eradication of the bacterium. In particular, some studies evaluated the effect of periodontal therapy on HP infection (7).

The re-infection rate of HP is high, even after the standardized treatment regimen eradicating HP from gastric mucosa. The oral cavity and peridontal pockets have been hypothesized as one of the suggested mechanisms of re-infection and the possible re-colonization. Some studies have also reported that the condition of chronic infection related to periodontal disease may also favor colonization of periodontal pockets by HP (8, 9).

However, the results are controversial. Different studies have found discrepant results, ranging from 0-100% positivity for HP in the oral cavity by polymerase chain reaction (PCR) methods (8, 9). In addition, inconsistent correlation between HP positivity in the oral mucosa and in the stomach has been found. Many factors likely account for this variability, including the genetic background of the study population, cultural habits, socioeconomic level and differences in the accuracy of the methods used as well as the strain of bacteria (8).

HP was detected in different niches of the oral cavity: periodontal areas, mucosa and saliva. High prevalence of HP was detected in the oral cavities of periodontitis patients (10). A positive link was observed between HP infection and periodontal disease, and an association was established between the supragingival colonization of HP and oral hygiene parameters, such as the presence of plaque and gingival bleeding (11).

The gastric infections caused by HP are treated with systemic therapy (antibiotics and proton pump inhibitors). The eradication of the infection reduces the risk of recurrence of gastric ulcers (12). However, relapse is always possible. In view of the difficulties in eradicating the bacteria in the stomach, it is essential to identify potential reservoirs of the bacteria that could be responsible for the refractoriness to therapy.

It has been shown that HP of the oral cavity is associated with recurrent gastric infection. Oral colonization of HP in dental plaque can persist after eradication therapy. Therefore, even if eradication therapy is successful, dental plaque might be a sanctuary for HP, leading to gastric recurrence (12). HP in dental plaque may represent a risk factor for gastrointestinal reinfection and ulcer relapse after antibiotic therapy. The periodontal pocket may be important as a natural reservoir for HP, because it can provide microaerobic conditions (13). Oral cavity of gingivitis or chronic periodontitis patients who are positive for HP in their stomachs can harbor HP after systemic eradication. Recently, a meta-analysis confirmed the close relation between infection of HP in the oral cavity and the stomach. HP in the oral cavity is more difficult to eradicate than in the

stomach, and may be a source of re-infection (13).

One of the keys to success related to the eradication of HP is represented by oral hygiene and periodontal therapy (14). Some studies have suggested that periodontal disease may be related to an increased risk of gastritis and gastric ulcers. Persistence of inflammation factors due to periodontal disease and alteration of gastrointestinal microbiome may be considered the associated cause of gastric diseases (15, 16).

Despite an association between HP and periodontal disease has not been demonstrated, the effectiveness of periodontal therapy on the elimination of HP is clinically relevant even if not well documented.

Recurrent aphthous stomatitis (RAS) and HP

Recurrent aphthous stomatitis (RAS) is a common condition that is characterized by multiple recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floor, with a wide range of reported prevalences from 5 to 50% in different populations. These ulcers appear on the non-keratinized (or less keratinized) oral mucosal tissues, and usually regress spontaneously within 14 days. The onset of these ulcers is usually during childhood, and they tend to diminish in frequency and severity with age. The frequent aphthous ulcers can increase the severity of patient discomfort and cause functional complications, including associated difficulties in speaking, brushing teeth and eating. The aetiology of aphthous lesions is still not clear. The histopathological changes in the preulcerative stage include infiltration of the epithelium by mononuclear (lymphocytic) cells; oedema develops, followed by keratinocyte vacuolization and localized vasculitis, causing localized swelling that ulcerates and is infiltrated by neutrophils, lymphocytes, and plasma cells before the healing phase and regeneration of the epithelium. These clinical and histological findings and the discovery of HP in RAS ulcers make this disease similar to gastritis and duodenal ulcers. Another important relationship between RAS and HP is the high incidence of anemia in patients with RAS that may be caused by HP-positive stomach disease. In fact, antibiotic therapy and treatment of anemia can reduce the frequency of RAS ulcer recurrence (17).

Oral cancer and HP

Oral cancer is the sixth most common cancer in the world, with approximately 350,000 deaths and 650,000 new diagnoses per year. It is estimated that more new cases will be diagnosed in developing countries. Risk factors for the development of oral cancer are many. Smoking: cigarette, cigar, or pipe smokers are six times more likely than non-smokers to develop oral cancers. Alcohol consumption: oral cancers are about six times more common in drinkers than in non-drinkers. Excessive sun exposure, especially at a young age, and family history of cancer are considered risk factors. Human papillomavirus (HPV): certain HPV strains are etiologic risk factors for oropharyngeal squamous cell carcinoma (OSCC) (18). Even if HP was considered a carcinogenic agent type 1 for stomach cancer by the International Agency for Research on Cancer, OMS/IARC, regarding the role of H.P in the etiology of squamous cell carcinoma, to date no evidence is available (18, 19).

CONCLUSION

There is evidence of relationship between oral and HP-related gastric diseases, in particular periodontitis, peri-implantitis, RAS and oral cancer. Both infections have in common their great diffusion in the world population. It is well known that the oral cavity is an extra-gastric reservoir of HP and that periodontal therapy associated with systemic therapy may better eradicate HP from the mucosa of all gastro-enteric tract, reducing the relapse of HP infection. Prospective cohorts studies are needed to reveal the bacterial action in the oral cavity.

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