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Chronic atrophic gastritis aggravate chronic periodontitis with *Helicobacter pylori* infection and CD4+Th cytokines infiltration

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Summary. Objective. To investigate the potential effect of chronic atrophic gastritis on chronic periodontitis and further explore the possible mechanism.

Methods. Local periodontal lesions were collected from periodontitis tissues of 30 CAG patients and 35 control adults without CAG (non-CAG). Clinical periodontal parameters were recorded, and the expression levels of distinct CD4+ Th specific cytokines at local periodontitis lesions were evaluated by real time PCR (RT-PCR). *Helicobacter pylori* (*H. pylori*) detection was carried out in both gastric and periodontitis lesions of CAG and non CAG patients.

Results. Clinical parameters analysis showed that the level of clinical attachment loss in periodontitis lesions of CAG group was significantly higher than non-CAG group. It was observed that the infection rate of *H. pylori* in the CAG group was higher than non-CAG group. Further cytokine analysis showed that Th17 associated cytokines IL-17, IL-21 and IL-23 were increased in periodontal lesions of CAG patients when compared with non-CAG patients. However, Th1, Th2, Th9 and Treg cells specific cytokines were not significantly increased in CAG group when compared with non-CAG group.

Conclusions. Patients with CAG demonstrated that significant elevated attachment loss in periodontitis lesions, while elevated Th17 cytokines IL-17, IL-21 and IL-23 participate in immunopathogenesis of both diseases.

Key words: Chronic atrophic gastritis, Periodontitis, cytokines, *Helicobacter pylori*

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Introduction

Chronic atrophic gastritis (CAG) is one of the most common gastric mucosal infectious disease, which is defined as the loss of gastric glandular structure or glandular structures metaplastic atrophy. The clinical symptoms include abdominal pain, fullness discomfort, occasional anemia and emaciation. Epidemiological studies demonstrated that the global incidence of CAG is about 0.5-10.9%, especially in Asia countries such as China and Japan (Liu et al., 2009; Adamu et al., 2010; Du et al., 2014). In recent years, it has been widely accepted that CAG is involved in *H. pylori* infection, making it easy to develop into an essential precursor lesion in the progress of gastric cancer (Plummer et al., 2007). A previous study showed that *H. pylori* infection has an apparent relationship with chronic gastritis and periodontal health (Navabi et al., 2011). *H. pylori* is an opportunist gram negative microorganism, which may lead to human gastrointestinal diseases via infected foods or water (Vale et al., 2010; Karimi et al., 2014; Wang et al., 2015). *H. pylori* can be present in oral saliva, tongue dorsum, and dental plaque as a suitable reservoir (Kobayashi et al., 2010). However, persistent

H. pylori infection may lead to its transformation into atrophic gastritis, intestinal metaplasia, dysplasia, and even gastric adenocarcinoma. Therefore, oral and periodontal status play important roles in the recurrence of gastric *H. pylori* infection.

Periodontitis is the most common chronic inflammatory oral disease with higher prevalence and multiple negative impacts on the quality of life, characterized by destruction of the supporting tissues around the teeth. Periodontitis is considered to be associated with plenty of human diseases such as diabetes mellitus (Engebretson et al., 2007; Preshaw et al., 2012), and rheumatoid arthritis (Kobayashi et al., 2010; Queiroz-Junior et al., 2011). Although the mechanisms by which periodontitis interacts with other diseases remain unclear, inflammation as a central feature may play a very important role in periodontal pathogenesis. A study showed that less tooth cleaning, leading to poor oral and dental hygiene, may be a risk factor with the frequent presence *H. pylori* infection (Liu et al., 2008). In addition, *H. pylori* in dental plaque can be reduced by anti-*H. pylori* therapy (Gebara et al., 2006). Therefore, *H. pylori* eradication from oral cavity can be considered as a comprehensive management measure involved in *H. pylori*-associated diseases (Bouziane et al., 2012). To date, the relationship between gastric pathology and oral hygiene has been reported in many studies (Salazar et al., 2013; Sun et al., 2017). A prior study has found that periodontal status was highly associated with CAG status (Boylan et al., 2014), meanwhile other research also indicated that the increased plaque and calculus deposits were correlated with an elevated incidence of gastric deterioration (Salazar et al., 2012). Considering the periodontal status in CAG patients, some researchers suggested that measures should be taken to reduce the frequency of periodontal disease in CAG patients (Mignogna et al., 2005).

Previous studies investigated that *H. pylori*-related gastric disease may be associated with significant inflammatory cytokines imbalance (Engebretson et al., 2007; Preshaw et al., 2012). It was found that Th17, Th22 and Th9 they can produce some specific cytokines, such as IL-17, IL-22 and IL-9 (Romagnani et al., 2009). The major role of IL-17 and IL-9 has been described in various models of autoimmune diseases and inflammation mediated destruction, such as rheumatoid arthritis or Crohn's disease (Yang et al., 2014). Therefore, CD4+ T cell subsets and cytokines may play important roles in inflammation response in CAG patients with periodontitis. To our knowledge, there are few reports focused on the association between CAG and periodontitis diseases with certain inflammatory cytokines, especially concerned with *H. pylori* infection (Vered et al., 2013). Thus, this study aimed to investigate the expression level of CD4+ T cell subsets and cytokines in stomach and local tissues of periodontitis patients with and without CAG to further explore the potential impact of chronic atrophic gastritis on chronic periodontitis.

Materials and methods

Subjects

All patients with CAG disease were enrolled from the department of Gastroenterology in Beijing Luhe Hospital, Capital Medical University. The study was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University. All patients signed the informed written consents and the entire experimental procedure was conducted in accordance with the Declaration of Helsinki. Histopathological examination and endoscopy were used to characterize CAG disease. Five samples were harvested from the patients with CAG, 2 samples from greater curvature of the stomach, 2 samples from gastric antrum and cardia, 1 sample from gastric angle. The samples must be marked clearly in order to make correct histopathological diagnosis for the pathologist. The periodontologist performed periodontal examinations and recorded clinical attachment loss, probing depth, Silness-Loe plaque and Loe-Silness gingival index. The loss of clinical attachment from the depth of periodontal pocket to the cementoenamel junction was recorded. The periodontal tissues were stored at -150°C.

H. pylori detection test

H. pylori was detected by diagnostic kits (Beijing Pharmaceutical Co, Ltd) and HG-IRIS13C infrared spectrometer. A positive result with the detected value in the exhalation must be not less than 4. Microbial DNA quantitative PCR Multi-Assay *H. pylori* Kit (Cat. no. 330043, Qiagen) was used to detect the positive reaction of periodontal tissues of two patients groups. The Multi-Assay Kit was used for the detecting virulence factor genes from *H. pylori*. The kit contains assays for detecting *H. pylori* itself and the virulence factor genes. A positive PCR control assay was used to test the efficiency of polymerase chain reaction. Identification of pathogenic *H. pylori* presence was accomplished using data analysis software with imported CT values generated by the PCR instrument software.

Hematoxylin and eosin staining

The tissue samples were fixed in paraformaldehyde and embedded in paraffin routinely. The paraffin blocks were cut into continuous sections of 5 μm. The sections were dewaxed with xylene and washed with 70%, 85% and 95% gradient alcohol. Subsequently, the sections were stained with hematoxylin and then differentiated, washed and stained with eosin. Finally, the sections were mounted on slides and observed under under the light microscope (Olympus, Japan).

Real-time quantitative PCR (RT-qPCR)

The total RNA of periodontal gingival tissues was extracted using Trizol (Invitrogen, Carlsbad, CA, USA) and purified using RNeasy Mini Kit (QIAGEN KK, Tokyo, Japan) according to the instruction handbook of the manufacturer. The absorbance of each sample was determined by the ultraviolet spectrometer to keep the purity of RNA between 1.8 and 2.0. The RNA was reversely transcribed to cDNA synthesized using cDNA reverse Transcription Kit (QIAGEN KK, Tokyo, Japan). The primer sequences of IL-17, IL-23, IL-22, IL-21, IL-9, IL-4, INF-γ, TGF-β and GAPDH were all purchased from TaKaRa CO, Ltd (Dalian, China). The thermocycling conditions were as follows: 95°C for 5 min; 30 cycles of 95°C for 30 s, 56°C for 30 s and extension at 72°C for 1 min. The relative quantities of mRNA were calculated using $2^{-\Delta\Delta Ct}$ method and normalized to the housekeeping gene GAPDH.

Statistical analysis

All data were analyzed with SPSS 15.0 (SPSS, Chicago, IL, USA) and are expressed as mean ± standard deviation. All detection data were normalized and analyzed by Student t-test, while variance of gender and *H. pylori* infection rate was evaluated by Chia-square test. Data distribution was assessed by the 1-sample Kolmogorov-Smirn test. P value <0.05 was considered statistically significant.

Results

Characteristic and periodontal parameters in periodontitis patients

All periodontal parameters and demographic characteristics in CAG and non-CAG group are listed in Table 1. Statistical results showed that there were no significant difference between CAG and non-CAG groups regarding gender and age (Table 1, P>0.05). Additionally, there were no significant difference between CAG and non-CAG groups regarding probing depth, gingival index and plaque index (Table 1, P>0.05). Compared with the non-CAG group, the clinical attachment loss was remarkably increased in patients with periodontitis in the CAG group (Table 1, P<0.05).

H. pylori infection in gastric and periodontitis

It was found that *H. pylori* infection of gastric in the CAG group was higher than non CAG group (Table 2, P<0.01). In contrast to non CAG group, the *H. pylori* infection rate of periodontal tissues in the CAG group was significantly increased (Table 2, P<0.01).

Histopathological examination and endoscopy characteristic of CAG patients

Fig. 1A-F is the endoscopic and HE staining figures of the CAG stomach. Fig. 1A is non-CAG with smooth

Table 1. Demographic characteristics and clinical parameters in chronic periodontitis patients with and without CAG.

Periodontitis patients	Non CAG Group (Mean ± SD)	CAG Group (Mean ± SD)
[a]Age (years)	47.5±10.5	51.4±12.7 NS
[b]Gender		
Female	20 (57.1%)	15 (50%) NS
Male	15 (42.9%)	15 (50%) NS
[a]Probing depth (mm)	4.8±1.3	5.2±1.6 NS
[a]Clinical Attachment loss (mm)	1.3±0.6	1.8±0.7*
[a]Plaque index	1.3±0.4	1.2±0.5 NS
[a]Gingival index	1.2±0.5	1.4±0.4 NS

[a]: Student t-test; [b]: Chi-square test; SD: standard deviation; *: P<0.05; **: P<0.01; NS represents no statistically significant difference (P>0.05).

Table 2. HP infection in gastric and periodontal lesions of chronic periodontitis patients with and without CAG.

Periodontitis patients	Total number (Male/female)	Gastric HP	Periodontal HP
Non CAG	35(20/15)	5(14.3%)	8(22.9%)
CAG	30(15/15)	15(50%)	20(66.7%)
CAG vs Non CAG[a]		**	**

[a]: Chi-square test; **: P<0.01.

Table 3. Primer sequences for the real-time quantitative PCR.

Target gene	Primer sequence	PCR product size
IL-17	F: 5'- aaccgatccacctcaccttg-3' R: 5'-tctcttgctggatggggaca-3'	154 bp
IL-23	F: 5'-ccttctctgctccctgatagc-3' R: 5'-gactgaggcttggaatctgct-3'	118 bp
IL-22	F: 5'-cgaccaggttctccttcccca-3' R: 5'-cagatttctgcagggcggcca-3'	75 bp
IL-21	F: 5'-actttatctcactgcccaactt-3' R: 5'-ttataaggggactgggggct-3'	506 bp
IL-9	F: 5'-tgacaactgcaccagaccat-3' R: 5'-gcatggctgttcacaggaaaa-3'	157 bp
IL-4	F: 5'-caagaatcctgctgcccatga-3' R: 5'-gtaaggaccccaccactcac-3'	89 bp
INF-γ	F: 5'-atggttgtcctgcctgcaat-3' R: 5'-cttgcttaggttggctgcct-3'	284 bp
TGF-β	F: 5'-acgaggtgcactcgagctt-3' R: 5'-ggtccagcatgaacatgggt-3'	153 BP
GAPDH	F: 5'- ctttggtatcgtggaaggactc-3' R: 5'-gtagaggcagggatgatgttct-3'	132 bp

mucosa showing hyperemic erythema. Correspondingly, Fig. 1D is the HE staining, in which chronic inflammation of the gastric mucosa, lamellar edema of the lamina propria, and infiltration of mucosal superficial lymphocytes can be seen. Fig. 1B is mild atrophic gastritis. In the figure, the gastric mucosa is rough, red and white, mainly white. Similarly, HE staining results revealed chronic inflammation of mucosal tissue with a slight decrease in the proper glands (Fig. 1E). Fig. 1C is severe atrophic gastritis, the color of the gastric mucosa is dark, the mucous membrane is thin, red and white, mainly white. Correspondingly, the pathological results of HE showed chronic inflammation of the mucosa, moderate intestinal epithelial metaplasia of the glandular epithelium, and proliferation of leukocyte tissue in the interstitial forest, and the gland was significantly reduced (Fig. 1F).

Real-time quantitative PCR

The results showed that the expression level of Th17 cell subsets and cytokines including IL-17, IL-23 and IL-21 was significantly increased when compared with non-CAG group (Fig. 2, $P<0.05$). However, the expression level of Th9, Th22 and Treg cells specific cytokines were no significant changes in two groups (Fig. 2, $P>0.05$). In addition, there was no significant difference between CAG group and non CAG group in terms of Th1 and Th2 specific cytokines (Fig. 3, $P>0.05$).

Discussion

A previous study demonstrated that oral conditions and gastrointestinal diseases were closely related in *H. pylori* of chronic gingivitis (Elizarova et al., 2006). Meanwhile, another study showed that tooth loss can significantly increase the risk of gastric cardia adenocarcinoma (Abnet et al., 2005), gastric precancerous lesions and *H. pylori* infection at stomach and periodontal lesions (Zahedi et al., 2017). In addition, a study further confirmed the relationship between chronic periodontal disease and gastric precancerous lesions, suggesting that the reduction of periodontal pathogens and oral bacterial diversity play an important role in decreasing development of precancerous lesions of the stomach (Salazar et al., 2013). Chronic periodontitis has been associated with a variety of systemic inflammatory diseases such as diabetes (Ide et al., 2011), rheumatism and tumors (Michaud et al., 2008; Boylan et al., 2014). Chronic inflammation, immune responses, and bacterial invasion were thought to be the

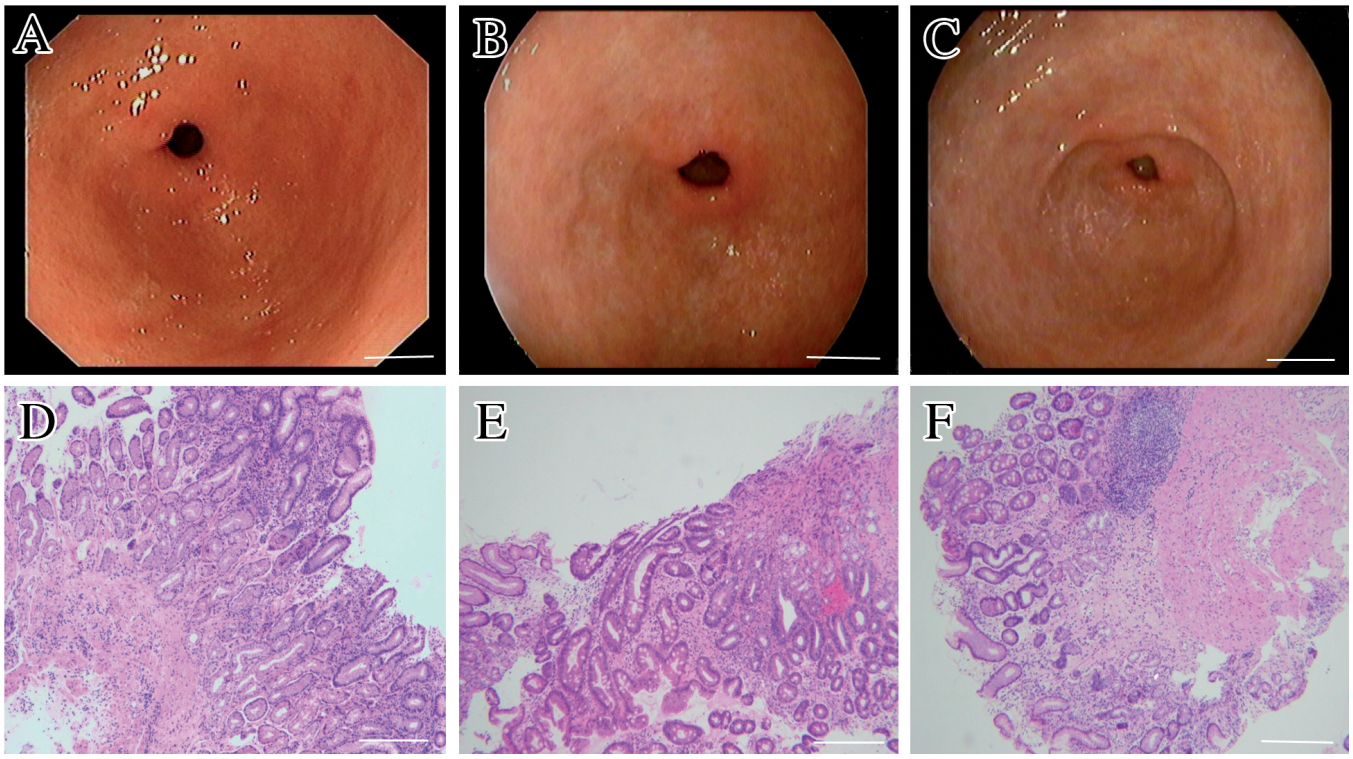

Fig. 1. Clinical gastric images and H&E staining of biopsy tissues in CAG patients. **A.** Gastric image of non-CAG patients. **B.** Gastric image of slight CAG patients. **C.** Gastric image of severe CAG patients. **D.** H&E staining of biopsy gastric tissues in non-CAG patients. **E.** H&E staining of biopsy gastric tissues in slight CAG patients. **F.** H&E staining of biopsy gastric tissue in severe CAG patients. Scale bars: 50 μm.

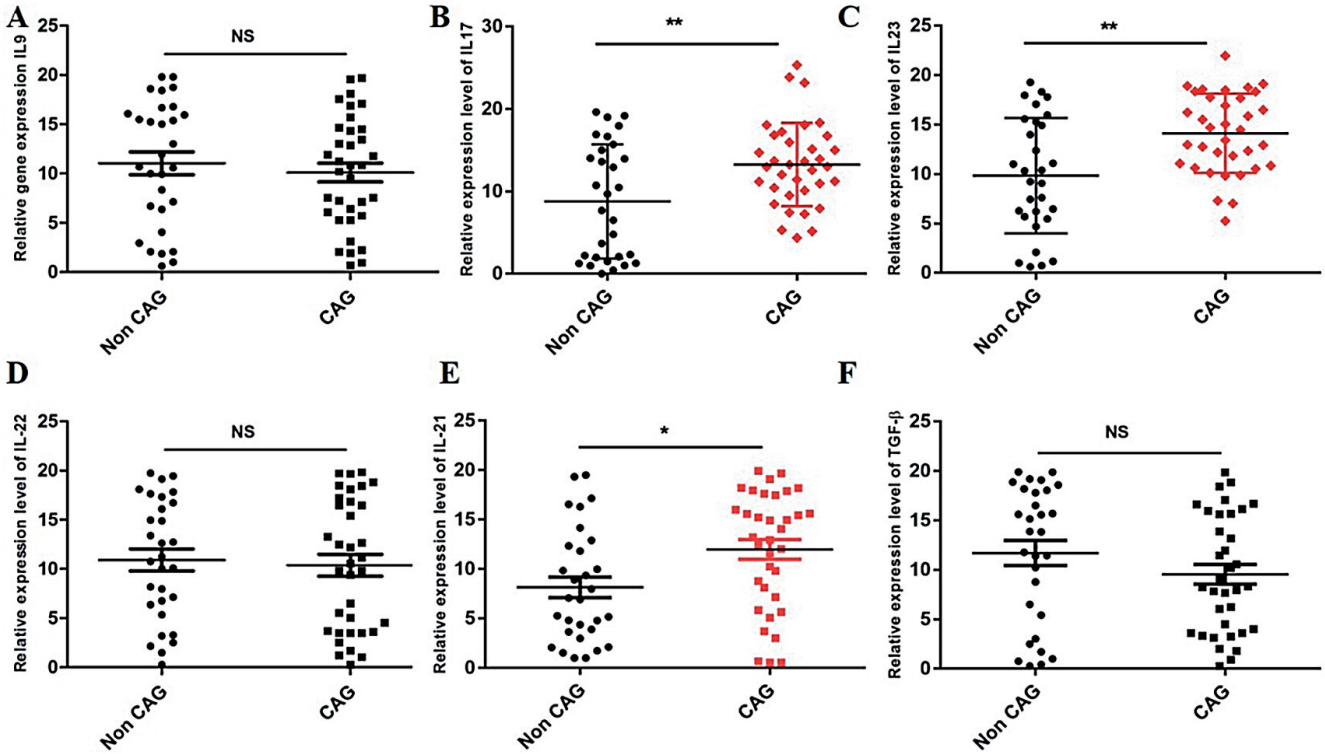

Fig. 2. Expression level of CD4+ Th subset Th9, Th17, Th22, and Treg cells with its specific cytokines in chronic periodontitis tissues of CAG and non CAG patients. Expression level of specific cytokines mRNA were assessed by RT-PCR. **A.** The relative expression of Th9 specific cytokine IL-9. **B.** Th17 specific cytokine IL-17. **C.** Th17 associated cytokine IL-23. **D.** Th22 specific cytokine IL-22. **E.** Th17 specific cytokine IL-21. **F.** Treg specific cytokine TGF-β. *: P<0.05; **: P<0.01.

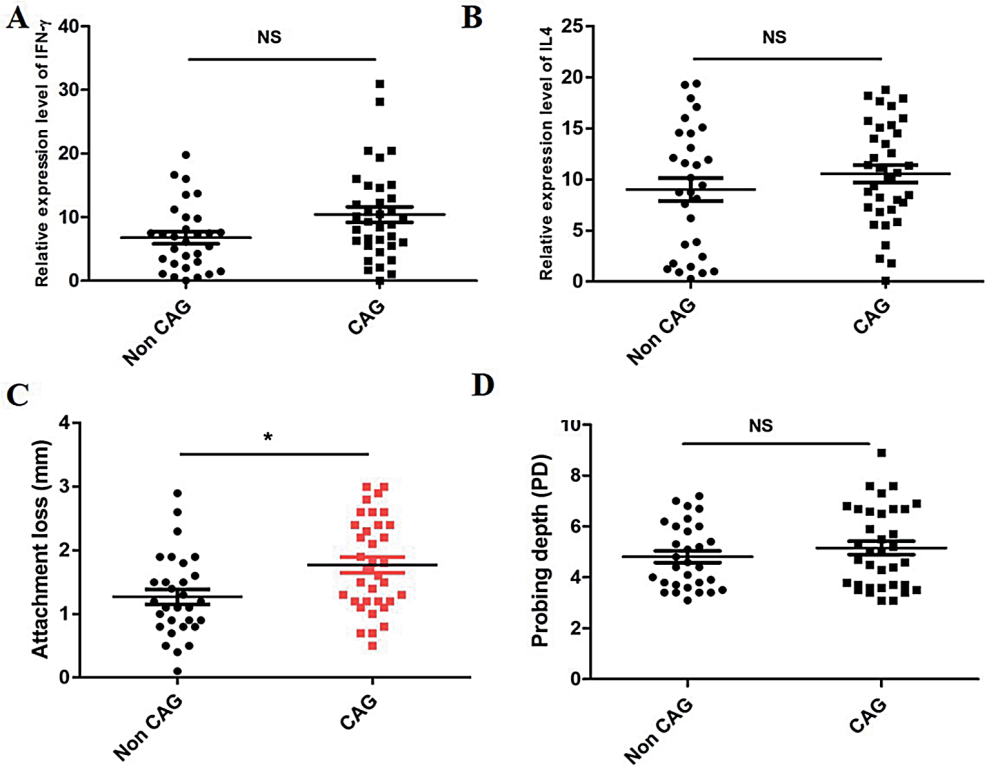

Fig. 3. Expression level of CD4+ Th subset Th1, Th2 with specific cytokines in chronic periodontitis tissues of CAG and non CAG patients .Clinical periodontal parameters of CAG and non-CAG patients were listed as follows, including clinical attachment loss and probing depth. Expression levels of specific cytokines mRNA levels were assessed by RT-PCR. **A.** Th1 specific cytokine IFN-γ. **B.** Th2 specific cytokine IL-4. **C.** clinical attachment loss. **D.** probing depth.

most important risk factors for those diseases (Abnet et al., 2001). Furthermore, a study confirmed that the plaque index was significantly associated with atrophic gastritis, severity of periodontal disease and gastric *H. pylori* infection histopathology (Liu et al., 2009). However, it remains uncertain whether chronic atrophic gastritis may affect periodontal disease yet. In this study, we found there were no significant differences in gender and age between the CAG group and the non-CAG group in patients with periodontal disease, and there was no significant difference in the depth of periodontal probing between the two groups. A further study found that the alveolar bone loss in CAG group was significantly higher than that in non-CAG group. There was no significant difference in plaque index and gingival bleeding index between the two groups. The above results indicated that periodontal destruction in the CAG group was significantly higher on the non-CAG group, suggesting that atrophic gastritis may significantly aggravate bone destruction in periodontal patients, resulting in persistent bone loss. However, it is unclear exactly how CAG will aggravate periodontal damage.

It was confirmed that *H. pylori* is the main pathogen leading to various types of chronic gastritis, and it is also a risk factor for early gastric cancer. *H. pylori* can be isolated from the oral cavity such as gingival and oral mucosal tissues and thus considered as the second reservoir in human (Li et al., 2016). Periodontal health and *H. pylori* colonization are closely related to patients with periodontal disease. The aforementioned findings indicated that patients with periodontal disease and tooth loss have a higher rate of *H. pylori* infection. In patients with chronic gastropathy, triple therapy of *H. pylori* in conjunction with periodontal treatment is more effective in improving *H. pylori* eradication rates. Gastric *H. pylori* infection is closely related to oral mucosal *H. pylori* location, because the stomach of *H. pylori* will go through gastroesophageal reflux and other pathways into the mouth to increase oral *H. pylori* infection. The higher presence of *H. pylori* aggravated the occurrence and development of oral diseases of the gastrointestinal tract. In this study, HP test results showed that the proportion of HP infection in the stomach was significantly higher in patients with CAG than in healthy controls. Endoscopic observation and HE staining results also confirm our conclusions. At the same time, HP infection in periodontal tissues was detected by tissue PCR, and the proportion of HP infection in periodontal tissues of patients with CAG was also significantly higher than that of normal control periodontal tissues. The above results showed that the proportion of HP infection in the stomach and periodontal tissue of CAG patients was significantly higher than that in the control group, suggesting that CAG in atrophic gastritis not only increased the proportion of HP infection in the stomach, but also may continuously aggravate the gastric infection through the bacterial reservoir of periodontal tissue. Therefore, in addition to the anti-infection treatment for the stomach, corresponding targeted treatment measures must be taken for oral infection, so as to achieve the maximum clinical radical treatment for the stomach HP.

It was observed that more severe periodontitis can produce elevated levels of cytokine IL-17 (Trombone et al., 2010; Luo et al., 2015). In the present study, enhanced expression level of IL-21 and IL-23 mRNA in periodontal lesions may indicate its involvement in CAG promoted periodontal destruction, but the specific mechanism of those cytokines in periodontal lesions remains unclear. In addition, a study showed that Th17 can produce cytokine IL-17 in an IL-23-dependent way (Luo et al., 2014), however it was not demonstrated that the expression of IL-17 or IL-23 in local periodontal lesions of CAG was significantly elevated. As indicated above, periodontitis is a chronic inflammation triggered by potentially hazardous microorganisms and the consequent immune-inflammatory responses, while CAG is also a chronic inflammatory gastritis disease and may trigger the periodontal tissue broke-down.

Conclusions

The patients with CAG demonstrated significant elevated attachment loss in periodontitis lesions. Th17 associated cytokines IL-17, IL-21 and IL-23 were increased in periodontal lesions of CAG patients when compared with non-CAG patients, suggesting that they may participate in the immunopathogenesis of both common diseases.

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Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions. WL and BX convecied the design. WL performed the writing of the manuscript. YL analyzed and interpreted the patient data. ZL collected and assembled the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate. The study was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University. All patients signed the informed written consents and the entire experimental procedure was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication. All patients provided written informed consent for the publication of any associated data and accompanying images.

Competing interests. The authors declare that they have no competing interests

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