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Research Paper

Prevalence of *Helicobacter felis* and *Helicobacter heilmannii* and Co-infection With *Helicobacter pylori* in Gastric Biopsy Specimens in Endoscopy Ward of Shahid Beheshti Hospital, Hamadan City, Iran

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ABSTRACT

Background: *Helicobacter pylori* (H. *pylori*) has various strains associated with human infections. H. *pylori*, H. heilmannii, and H. *felis* are the most common strains in humans. H. *pylori* is associated with several human diseases such as chronic gastritis, peptic ulcer, mucous membrane lymphoma, and gastric adenocarcinoma. This study aimed to determine the prevalence rates of H. *felis* and H. *heilmannii* and the effect of co-infection with H. *pylori* in gastric biopsy specimens of patients.

Methods: Totally, 80 gastric biopsy specimens were taken by a physician from the patients referred to Shahid Beheshti Hospital, Hamadan City, Iran. PCR test was used to confirm the presence of H. *pylori* in samples that had positive rapid urease tests. Moreover, the ureB gene and ureA and ureB genes were used for H. *heilmannii* and H. *felis*, respectively.

Results: Of the study patients, 61.5% were females, and 38.5% were males with a mean age of 37.8 years. Of 80 biopsies, 50% were H. *pylori*-positive, 53.8% were H. heilmannii-positive, but no H. *felis* was identified in any sample. Results indicate that smoking, having a history of gastrointestinal diseases, and taking certain medications can be risk factors for H. *pylori*.

Conclusion: Any agent contributing to gastric mucosal damage can enhance the susceptibility to bacterial contamination. Overall, the results indicate a low probability of interactions between H. *pylori*, H. heilmannii, and H. *felis*.

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1. Introduction

Helicobacter is a gram-negative bacterium. *Helicobacter pylori* (H. *pylori*) infects approximately half of the world's population, and its infection rate is higher than 70% in developing countries. Helicobacter strains (including H. *pylori*, H. heilmannii, H. *felis*, and several other species) cause human infections [1]. H. *pylori* is associated with various health problems in humans, such as chronic gastritis, peptic ulcer, mucous membrane lymphoma, and gastric adenocarcinoma [2-5]. Moreover, previous studies have shown a relationship between H. *pylori* infection and ischemic heart diseases, diabetes mellitus, anemia, and insulin resistance.

Another species of Helicobacter is H. *felis*, which can be found in the gastrointestinal tract of pets, especially cats. H. *felis* as a close relative of H. *pylori*, was first isolated from the stomach of a cat and considered a pathogen to domestic animals but was later isolated from human infections [6]. Studies in European countries have shown that H. *felis* has a low prevalence in humans (about 10%). However, there is also a higher level of contamination in some societies with higher contact with animals [7]. H. *heilmannii* is another species of Helicobacter, formerly known as Gastrospirillum hominins, with a lower prevalence than H. *pylori*. H. *heilmannii* was first discovered in 1987 [8].

It has been estimated that the global prevalence of this bacterium is between 0.2% and 1.7%. H. *heilmannii* causes chronic gastritis, gastric cancer, and tissue destruction. Unlike H. *pylori*, it is not exclusive to humans and infects many hosts such as cats, dogs, pigs, and primates, and hence is considered a zoonotic infection. The infection rate and prevalence of this bacterium in animals, unlike humans, is between 80% and 100%. In most cases, human infections with H. *heilmannii* result from direct or indirect contact with animals. Studies on the genome sequence of this bacterium indicate that the human and animal infecting strains are very similar to each other, which may indicate the direct transmission from animals to humans or vice versa. H. *pylori* is primarily transmitted through the oral-oral and oral-fecal epidemiological routs. H. *pylori* is isolated from dental plaque, vomiting, and possibly saliva, and the most important epidemiological pathway is the consumption of contaminated water and food products [9, 10]. By introducing this bacterium as a major cause of chronic active gastritis, researchers paid more attention to it. Nowadays, the role of this bacterium has been proven in various gastrointestinal diseases, such as indigestion, gastric ulcer, duodenal ulcer, gastric cancer, and gastric lymphoma [11, 12].

In recent years, H. *pylori* infection has become a growing public health concern in developing and developed countries. Genetic and environmental factors play an essential role in developing the diseases caused by H. *pylori*. Infection in early childhood leads to severe inflammation and progression of gastric mucosal atrophy, gastric ulcer, and gastric cancer. While infection in adults causes another type of gastric change that can eventually result in a duodenal ulcer. Moreover, a high rate of gastric cancer has been reported in areas where infection occurs more in early childhood [13]. International Organization for Research on Cancer (IARC) has identified H. *pylori* as a group 1 carcinogen (definite carcinogen). On the other hand, gastric cancer is the fourth most common cancer and the second leading cause of death in the world [14]. Recent studies have demonstrated that more than 90% of people with advanced adenocarcinoma in developing countries were infected with H. *pylori*, and over 80% of the population were carriers [15, 16].

Co-infection with two strains of Helicobacter may affect pathogenesis and antibiotic resistance, although this association is still controversial [6]. Different strains of Helicobacter have been isolated from gallbladder and gallstones in patients with benign gallbladder disease. Given the adverse effects of H. *pylori* infection, it is necessary to identify and eradicate the H. *pylori* infection in people. PCR and sequencing tests are commonly used as standard methods for the identification of these bacteria [16]. Therefore, this study aimed at determining the prevalence rates of H. *felis* and H. *heilmannii* and the effect of co-infection with H. *pylori* in gastric biopsy specimens of patients referred to Endoscopy Ward of Shahid Beheshti Hospital, Hamadan City, Iran.

2. Materials and Methods

In this cross-sectional study, 80 gastric biopsy specimens were collected from patients referred to Shahid Beheshti Hospital in Hamadan, west of Iran.

This study was approved by the Research Ethics Committee of Hamadan University of Medical Sciences (Code: IR.UMSHA.REC.1395.380). Ethical considerations, such as keeping personal information private, were observed during the conduction of this study. This study was conducted in accordance with the Declaration of Helsinki. The gastric biopsy specimens were taken by a physician and transferred to the Microbiology Laboratory of the Hamadan University of Medical Sciences.

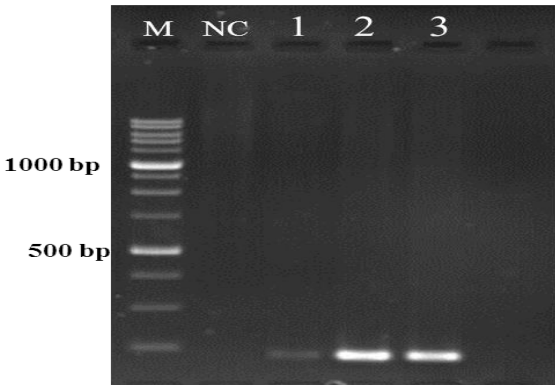

Figure 1. Gel electrophoresis of PCR products for *H. pylori*

(M lane: marker 100 bp, NC lane: negative control and lanes 1-3: positive samples)

The inclusion criteria were patients with a history of abdominal pain, lab-confirmed patients for H. *pylori* with unsuccessful routine treatment, patients with gastralgia without a history of stomach diseases, and patients with a history of abdominal pain without lab confirmation for H. *pylori*. The exclusion criteria were patients with active infectious diseases, patients who received antibiotics, and those under chemotherapies.

The urea medium was prepared for a rapid urease test. After sampling, one of the samples was immediately placed in a microtube containing urea. The change of urea color from yellow to purple during 2-4 hours indicated the test positive. Another specimen was placed in a microtube containing the transport medium (glycerin and BHI), and both of them were transferred into the microbiology laboratory. The specimens placed in the transport medium were then cultured on an egg-enriched brucella agar medium. Eventually, the samples were placed in a transport medium and stored in a freezer at 70˚C [15, 17].

Columbia agar (Merck-Germany) medium enriched with 10% FBS and 10% lysed sheep blood was used for bacterial culture. The bacteria were then cultured in a jar containing Anaerocult® A (reagent for generating an anaerobic medium in anaerobic jars) [18].

DNA extraction

DNA extraction was conducted using the Bioneer AccuPrep Genomic DNA Extraction Kit, according to the manufacturer's instructions. The extracted DNA was then stored at -20°C until further use.

PCR test

PCR test was used to confirm the presence of H. *pylori* in samples with a positive urease test. The primer sequence was as follows.

Helicobacter primers and temperature program

The master mix was prepared in a final volume of 25 µL, including 12.5 µL of the master mix, 0.5 µL of each forward and reverse primers, 4 µL of DNA template, and 7.5 µL of distilled water. Thermo-cycler temperature program for this gene was as follows: 3 min at 95˚C, 30 s at 95˚C, 30 s at 56˚C, 30 s at 72˚C, 5 min at 72˚C, and finally, 5 min at 4˚C. The primers used and the size of amplified fragments of ureC, ureB, and ureA and ureB genes are presented, respectively (Table 1-3).

3. Results

In this study, the patients were between 17 and 80 years old, with a mean age of 37.8 years. Of them, 61.5% were females, and 38.5% were males. Of all participants, 19.2% were employed, 19.2% self-employed, 6.4% students, 46.2% housewives, 3.8% unemployed, and 5.1% farmers. Also, 7.7% of the participants had a history of alcohol abuse, and 17.9% were smokers. Among the patients, 55% had a history of gastrointestinal disease, and 2.6% had a specific disease. Among 80 patients studied, 37.2% of people took specific medications, and 52.6% were positive for the urease test.

In terms of diet, 1.3% of the patients had a protein diet, 2.6% plant-carbohydrate, 30.8% carbohydrate-protein, 55.1% protein-plant, and 60.3% had no specific diet. Of the 80 biopsy specimens, 50% were H. *pylori*-positive and 53.8% H. *heilmannii* positive. Also, H. *felis* was detected in none of the samples.

Table 1. Primers used and size of amplified fragments of ureC gene

Gene	Primers	Size of PCR products
ureCF	CAT CGC CAT CAA AAG CAA AG	214
ureCR	CAG AGT TTA AGG ATC GTG TTA G	214

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Table 2. Primers used and size of amplified fragments of ureB gene

Gene	Primers	Size of PCR products
UreB-F	GGG CGA TAA AGT GCG CTT G	580
UreB-R	CTG GTC AAT GAG AGC AGG	580

Table 3. Primers used and size of amplified fragments of ureA&B gene

Gene	Primers	Size of PCR Products
ureA&B-F	ATG AAA CTA ACG CCT AAA GAA CTA G	1148
ureA&B-R	GGA GAG ATA AAG TGA ATA TGC GT	1148

Table 4. Background conditions of patients with of H. *pylori* and H. *heilmanii* infection

	%					
Bacterial Names	Alcohol Consumption	Smoking	Gastrointestinal Disease History	Particular Disease History	Taking Specific Medicines	Urease
H. *pylori*	10.3	12.8	56.4	2.6	23.1	17.9
H. heilimanii	4.8	16.7	52.4	4.8	38.1	57.1

Of the 80 biopsy specimens examined in this study, 50% of the specimens were H. *pylori*-positive. Besides, 71.8% of the positive samples were isolated from female patients, and 28.2% were isolated from male patients. There was a significant relationship between gender and H. *pylori* infection (P=0.06). The youngest person with H. *pylori* infection was 17 years old, and the oldest was 56 years old. The mean age of patients with H. *pylori* infection was 36.2 years, and there was a significant relationship between age and H. *pylori* infection (P<0.05).

Of the studied samples, 53.8% were H. *heilmannii* positive. Also, 69% of the positive samples were isolated from female patients and 31% from male patients. The youngest person with H. *pylori* infection was 16 years old, and the oldest was 72 years. The mean age of H. *heilmannii* patients was 39.07 years, and there was no significant relationship between age, gender, and H. *heilmannii* infection (P>0.05). In this study, H. *felis* was not isolated from the specimens.

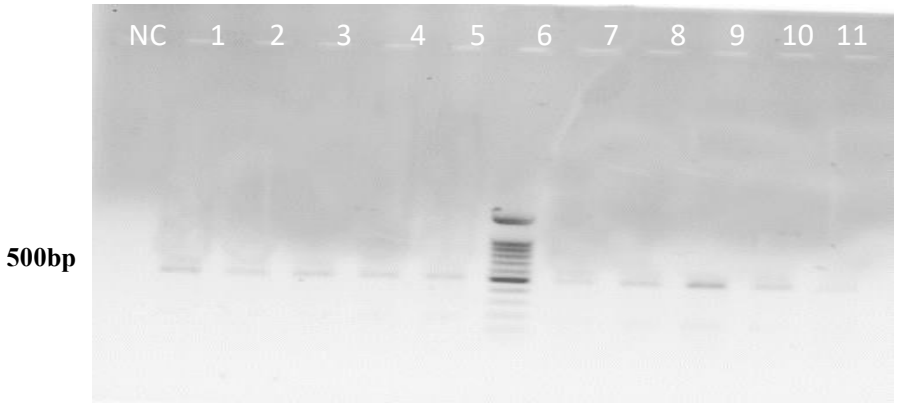

Figure 2. Gel electrophoresis of PCR products for H. *heilmanii*

(NC lane: negative control, lanes 1-5: positive sample, lane 6: marker 100 bp, lanes 7-11: positive sample).

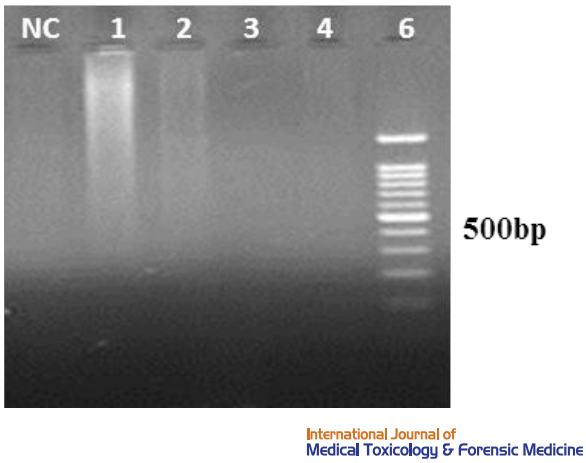

Figure 3. Gel electrophoresis of PCR products for H. *felis* (NC lane: negative control).

This study indicated that most patients with H. *pylori* and H. *heilmannii* infection were homemakers with frequencies of 53.8% and 47.6%, respectively. Nevertheless, there was no statistically significant relationship between them. Gel electrophoresis of PCR products for *H. pylori,* H. *heilmani,* H. *felis,* and H. *pylori* were presented in Figures 1-4.

Table 4 presents the background conditions of the patients. According to the results, there was a significant relationship between the prevalence of H. *pylori* and having a history of gastrointestinal diseases (P<0.05), using certain medications (P<0.05), and a positive rapid urease test (P<0.05). Nevertheless, there was no significant relationship between these parameters and H. *heilmannii* in the studied samples.

In this study, 82.1% of all H. *pylori* samples were negative, and 17.9% were positive for the rapid urease test. In contrast, 12.8% of the H. *pylori*-positive samples were negative, and 87.2% were positive for the rapid urease test.

Prevalence of co-infection with H. *pylori* and H. heilmannii

This step demonstrated that 48.7% of H. *pylori*-negative samples were negative, and 51.3% were positive for H. *pylori*. In contrast, 43.6% of H. *pylori* positive samples were negative for H. *heilmannii* and 56.4% were positive for H. heilmannii. Therefore, of all 80 biopsy specimens, 56.4% of patients had co-infection with H. *pylori* and H. heilmannii. However, this finding was not statistically significant.

4. Discussion

Given the widespread impacts of bacteria on human health, it is necessary to investigate their interactions with the environment and conditions that suppress or accelerate their growth and pathogenesis. In this regard, bacterial interactions with the surrounding bacteria to feed and transmit antibiotic resistance genes have received much attention from scientists [19]. This study aimed to determine the prevalence rates of H. *felis* and H. *heilmannii* and the effect of co-infection with H. *pylori* in gastric biopsy specimens of patients referred to Shahid Beheshti Hospital in Hamadan Province, Iran.

In the present study, H. *pylori* was identified in 50% of the patients. In Joo et al. study, H. *pylori* was observed in 55% of the patients, and there was no significant relationship between the presence of H. *pylori* and H. heilmannii, which is consistent with our findings [20]. However, in Yakoob et al. and Fritz et al. studies, H. *pylori* was identified in 6% and 23% of the cases, respectively. De-

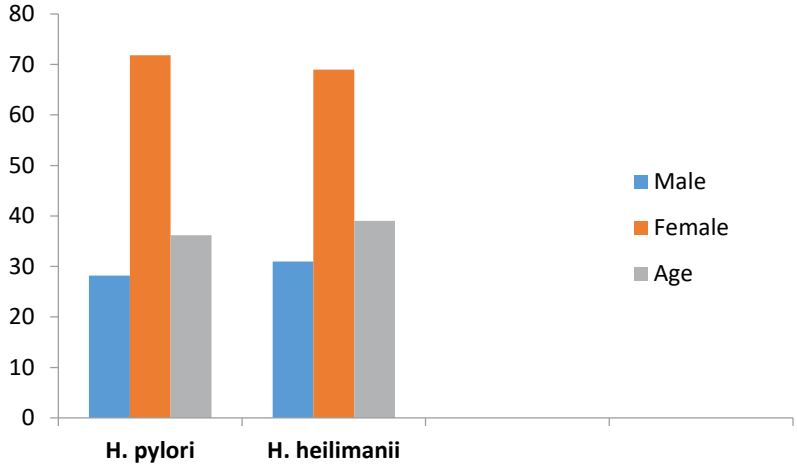

Figure 4. Frequency distribution of H. *pylori* according to age and gender

spite decreasing the prevalence of H. *pylori* in the world, the prevalence of this bacterium has been estimated to be 70%-90% in developing countries [1, 21].

In the present study, 53% of the patients were infected with H. heilmannii, which is more prevalent than in similar studies. This result can be due to the cultural differences and less contact of Iranian people with animals, especially cats and dogs. In agreement with these results, Fritz et al. reported a significant prevalence of H. *felis* among the African population compared with the European population. However, in the present study, the high prevalence of infection with H. *pylori* and H. *heilmannii* indicate that the universities and health centers must pay more attention to preventing and treating this infection [6].

In this study, the co-infections with H. *pylori*, H. heilmannii, and H. *felis* were studied to investigate the possible effect of bacteria on each other. The results showed co-infection with H. *pylori* and H. *heilmannii* in 56% of the cases, which is not sufficient to confirm their simultaneous presence and their interaction effects on each other in gastrointestinal diseases. These findings are consistent with the findings of the Yakoob et al. study [1]. Previous studies have reported a lower percentage of H. *pylori* than H. *heilmannii* in patients with gastritis and gastric ulcers, which indicated that H. *pylori* is the main cause of gastritis and stomach ulcers. The difference between our results and the findings of previous studies can be attributed to the difference in the statistical population. In Yang et al., Ierardi et al., Joo et al., and Boyanova et al. studies, the study patients were admitted to hospital for different health disorders such as gastritis and other gastrointestinal problems. Therefore, the high percentage of H. *heilmannii* infection in homemakers can be studied in future studies [15, 20-22].

5. Conclusion

In the present study, the prevalence rates of H. *felis* and H. *heilmannii* and the effect of their co-infection with H. *pylori* were studied in gastric biopsy specimens of patients. According to the results, various factors such as smoking, a history of gastrointestinal diseases, and taking certain medications are risk factors for H. *pylori*, which have been confirmed in previous studies. Therefore, any agent contributing to gastric mucosal damage can enhance the susceptibility to bacterial contamination. Overall, the results of this study indicated a low probability of interactions between H. *pylori*, H. heilmannii, and H. *felis*. However, due to the simultaneous presence of two or more bacteria, further studies are required to confirm their interactions.

Ethical Considerations

Compliance with ethical guidelines

This study was derived from a research project approved by the research and technology deputy of Hamadan University of Medical Sciences (project 9605173245) and Compliance with ethical guidelines (IR.UMSHA.REC.1395.380).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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