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Correlation between H. pylori infection and COVID-19 among a sample of dental students

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ABSTRACT

Objectives: COVID-19 infection, the most prevalent deadly pandemic in the world, has been correlated to the highly prevalent Helicobacter Pylori (H.P.) infection which is considered a major cause for gastric carcinoma and it seems to be an important risk factor that predisposes and augments the course of COVID-19 infection, via increasing the expression of angiotensin-converting enzyme-2 receptors in the gastrointestinal tract, to which COVID- 19 binds to enter the cell, causing gastrointestinal symptoms during the course of the disease. **The aim of this study** was to investigate any possible correlation between H. pylori infection and COVID-19 among a sample of dental students, at the faculty of Dentistry, Fayoum University, Egypt. **Methods & Subjects:** This study was carried out from October to November, 2022 among a sample of 100 dental students. Those who reported the characteristic symptoms of COVID-19 infection and whose infection was confirmed by nasopharyngeal (NS) PCR-RT swabs, were included in the study. All students were screened for anti- H.P. using saliva samples, analyzed with an enzyme-linked immunosorbent assay (ELISA). All were evaluated for manifestations of COVID-19 infection, severity of the course, hospitalized days because of the virus and outcome of the disease process. **Results:** Of 60 COVID-

19 positive patients evaluated, 41(68.3%) were H pylori-positive. There was significant correlation between the occurrence of GIT symptoms during the acute phase of COVID-19 and H.P. +ve cases (P=0.004). There was also statistically significant correlation between the presence of oral symptoms and H.P. +ve cases (p=0.05). Upon analysis of the severity of COVID-19 infection among H.P. +ve and –ve students, there was statistically significant correlation (p=0.027) in which 100% of severe, 77.4% of moderate and 50% of mild cases were H.P. +ve. The occurrence of classical COVID-19 symptoms among H.P. +ve individuals was significantly higher for fever, dry cough, dyspnea and loss of taste/smell sensation than H.P.-ve cases (P=0.022, 0.026, 0.035 and 0.007 respectively) **Conclusion:** Our results revealed a correlation between COVID-19 and H.P. infection, also between H.P. infection and the presence of oral symptoms. It seems that H.P. infection represents a risk factor affecting the course and outcome of COVID-19 infection with possible association with oral manifestations.

Keywords: *Helicobacter pylori, Coronavirus 19, Gastrointestinal tract.*

INTRODUCTION

Helicobacter Pylori (H.P.) infection is one of the most prevalent infections worldwide. It is widely spread out in more than half of the world's populations with the highest prevalence in developing countries. It has been documented that the global prevalence of H.P. is more than 5%, with a prevalence rate above 70% in Africa which is the highest worldwide and about 53% in Egypt (1-4).

H.P. bacterium is a gram-negative, microaerophilic and spiral-shaped bacillus. It is highly motile due to its multiple flagella with a high rate of survival in the stomach due to its microaerophilic properties (5).

H.P. infection is considered a major cause of gastric carcinoma owing to its contribution in creating a chronic state of inflammation which initiates and promotes atrophic gastritis to further intestinal metaplasia (IM) and thus, gastrointestinal (GI) carcinogenesis. The clinical presentation and severity of H.P. infection are related to virulence factors of the bacterium as well as host immune response (6).

COVID-19 (SARS-COV-2) infection was initially identified in Wuhan, China in December 2019. In a short time, on 11th March 2020, the WHO declared COVID-19 as a pandemic that was responsible for death of thousands of people all over the world (7).

Despite the enormous efforts to understand the pathophysiology of the COVID-19 pandemic, the complete comprehension of risk factors and management is not yet established. The disease pathogenesis involves organ damage caused by direct viral attack and exaggerated immune response. It has been reported that the virus gains entry to the cell by binding to angiotensin converting enzyme inhibitor-2 (ACE-2) receptors which are widely spread in the intestine (8, 9).

The widespread and high prevalence H.P. infection makes its interplay and co-existence with COVID-19, the most important infection in the world, an interesting topic for research. The prevalence of H.P. varies significantly according to geographic area, ethnicity and age. These variations are largely dependent on socio-economic and cultural differences among different populations (3, 10, 11).

The question arises about the transmission and persistence of H.P. infection, which is thought to occur mainly by oral-oral or oro-fecal route. Thus, lack of proper hygiene and sanitation, safe drinking water, poor diet as well as overcrowding are considered risk factors affecting overall disease prevalence. The available evidence suggests that the oral route is the main route for H.P. infection (10, 12-14).

To date, many researchers identified H.P. in dental plaque and saliva. On the other hand, some researchers found that, although H.P. has been eliminated from the stomach after treatment, it persisted in dental plaque and saliva and was responsible for recurrence of the disease (15-17). In that sense, some researchers examined the correlation between H.P. infection and oral manifestations with contradicting results (16).

Since COVID-19 infection is the most prevalent deadly pandemic in the world and has been correlated to

the highly prevalent H.P. infection which is considered a major cause for gastric carcinoma and it seems to be an important risk factor that predispose and augment the course of COVID-19 infection, this rationalizes the importance of investigating the prevalence of these two diseases in Egyptian populations with variable socio-economic and cultural backgrounds.

In the light of this possible relation between COVID-19, H.P. and oral manifestations, the present study was carried out on dental students in Fayoum University.

SUBJECT AND METHODS

A Declaration of Ethics

The aim of the study and its benefits were explained to each participant with emphasis on confidentiality of the collected data. Each participant signed an informed consent before being enrolled in the study. The study was approved by the local Ethical Committee (EC 2217).The study is complying with the Declaration of Helsinki for Medical Research involving Human Subjects.

Study design and setting

This observational cross-sectional study was conducted at Fayoum University, Faculty of Dentistry in Fayoum, Egypt.

Participants and conditions for eligibility

From October to November 2022, 100 students at Fayoum University Faculty of Dentistry were screened for a history of COVID-19 infection over the period of two months. Students who reported the characteristic symptoms of COVID-19 infection, including fever, dry cough, dyspnea, headache, malaise, and loss of taste and smell sensation, and whose infection was confirmed by nasopharyngeal (NS) PCR-RT swabs, were included in the study. Exclusion criteria were past H.P. eradication therapy, a history of gastric cancer, and negative NS PCR-RT findings.

Variables and data sources/measurement outcomes

All participants completed a systematic questionnaire to collect data. It included information such as age, gender, nationality, socioeconomic status, childhood living situations (rural or urban), systemic medical condition, previous H.P. infection and presence of H.P. among family members

The following complaints were recorded: nausea, vomiting, abdominal pain, and diarrhea. In addition, the existence of medical diseases such as hypertension and diabetes mellitus, as well as the medications used to treat these conditions, were analyzed for each patient.

According to the severity of the condition, patients were classified as mild (no pneumonia and no hospitalization), moderate (hospitalized without pneumonia) or severe (hospitalized with pneumonia). We evaluated the clinical features of COVID-19 in H.P. positive and-negative patients.

The detection of human H.P. antibody IgG (HP Ab IgG) in saliva (using ELISA kit)

All subjects were screened for anti- H.P. using saliva samples obtained in saliva collection vials (2-3 mL unstimulated whole saliva) and analyzed with an enzyme-linked immunosorbent assay (ELISA). Immune serum globulins for Helicobacter P. are produced in the Clinical Laboratory of the Medical School. Individuals who tested positive were instructed to undergo a confirmatory test (PCR) and receive medical care to confirm the diagnosis of H.P. infection.

This kit, which can be identified by its catalogue number, was provided by the Bioassay Technology Laboratory BT LAB (Zhejiang, China) (ED4123Hu). This kit employs a reverse-phase enzyme immunoassay technique for qualitative analysis, which is very sensitive and specific. Antigen of interest is already present on the microtiter plate. The wells are then incubated with a positive or negative control sample. Antibodies in the sample react with the antigen in the well. When the antibody has been bound, the sample must be washed to eliminate any unbound antibody. A detecting antibody coupled to horseradish peroxidase is used to treat the mixture (HRP). The washing procedure eliminates unbound HRP. The incorporation of a TMB substrate alters the colour. With the addition of an acidic stop solution, the color changes to yellow with a wavelength of 450 nm, concluding the process. After determining the optical density (OD) of the positive and negative controls, the presence of Hp Ab IgG can be verified by comparing the OD of the unknown sample to these values.

Sample size estimation

Based on prior research by Balamtekin et al.(18) that explored the effect of H.P. on the presentation and clinical course of Coronavirus disease and by comparing the proportion of H.P. positive to H.P. negative cases among COVID-19 patients using Fisher's exact test, calculations yielded the need for 60 students to achieve statistical significance at the 5% α risk of error and a 90% power (1-β risk of error). The application G*Power 3.1.9.7 was used to determine the sample size needed for the study.

Statistical methods

Most of the data in this study were qualitative (categorical) data, which were converted to percentages, and Chi-square and Fisher exact tests were used for statistical analysis. P-value <0.05 was considered

statistically significant. The Jamovi project (2022) (Version 2.3) [Computer Software] was used for all statistical analyses.

RESULTS

Among 100 students that were screened over a period of two months at the Faculty of Dentistry, Fayoum University, 60 students reported prior COVID-19 infection with its classical manifestations that has been confirmed with NS-RT-PCR. Based on the presence or absence of pneumonia and/or hospitalization (as previously described), 24% were considered mild, 31% were moderate and 5% suffered from a severe condition.

As shown in table (1), the included students were 41(68.3%) Egyptians, 19 (31.7%) non-Egyptians, 40(66.7%) females and 20(33.3%) males. Based on their socioeconomic status, 42(70%) were considered good and 18(30%) were moderate. Also, the majority of them 48 (80%) spent their childhood in rural areas, while 12 (20%) had their childhood in urban areas. Only 5(8.3%) students reported presence of systemic medical condition.

Although only 12 (20%) students reported history of previously diagnosed H.P., however, ELIZA results revealed that 41(68.3%) were positive H.P. cases, whereas 19(31.7%) were negative for H.P. In addition, 3 (5%) students reported the presence of H.P. infection among their family members.

According to participants' demographic data, there was no statistically significant correlation between +ve and –ve H.P. cases except for the childhood living condition in which the majority of 36 (75%) of +ve H.P. students were from rural areas, whereas only 5 (41.7%) were from urban areas (P value=0.039). Also, those who gave history of previously diagnosed H.P. were significantly greater in number among H.P. +ve than H.P. –ve (0.012).

Table (1): Patient characteristics

		H_pylori_ELIZA			
		positive	Negative		
		N=41 n(%)	N=19 n(%)	Total (n)	P value*
Nationality	Egyptian	25(61)	16(39)	41(68.3%)	0.072
	Non-Egyptian	16(84.2)	3(15.8)	19(31.7%)	
Gender	Female	28(70)	12(30)	40(66.7%)	0.695
	Male	13(65)	7(35)	20(33.3%)	
Socioeconomic status	Good	30(71.4)	12(28.6)	42(70%)	0.431
	Moderate	11(61.1)	7(38.9)	18(30%)	
Childhood Living conditions	Rural	36(75)	12(25)	48(80%)	**0.039[a]**
	Urban	5(41.7)	7(38.9)	12(20%)	1[a]
Medical health problem	Yes	4(80)	1(20)	5(8.3%)	0.336
History of previously diagnosed H.pylori infection	Yes	12(100)	0(0)	12(20%)	**0.012[a]**
History of H.pylori infection among family members	Present	3(100%)	0(0)	3(5%)	**0.545[a]**
GIT symptoms during acute phase of the disease (epigastric pain, postprandial fullness, regurgitation, fasting discomfort, heartburn, abdominal and esophageal reflux, burping, flatulence and frequent diarrhea, nausea and vomiting)	Present	31 (81.6%)	7(18.4%)	38(63.3%)	**0.004**
Persistence of GIT symptoms after other COVID-19 symtoms recovery	Yes	12(92.3)	1(77)	13(21.7%)	**0.045[a]**
Oral symptoms (oral dryness, oral ulceration, symptoms of gingival and periodontal diseases and halitosis)	Present	17(85)	3 (15 %)	20(33.3%)	**0.05**

P<0.05 is statistically significant, analysis done by Chi square test, a: analysis done by fisher exact test

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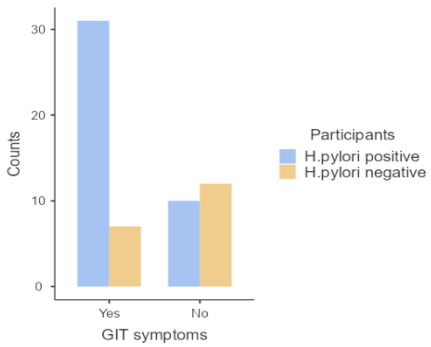
Moreover, there was significant correlation between the occurrence of GIT symptoms during the acute phase of COVID-19 and h.P. +ve cases (P=0.004). Similarly, the persistence of GIT symptoms after recovery of other COVID-19 symptoms was statistically evident among h.P. +ve than h.P. –ve cases (p=0.045). Additionally, there was statistically significant correlation between the presence of oral symptoms and h.P. +ve cases (p=0.05) as shown in **figures (1,2).**



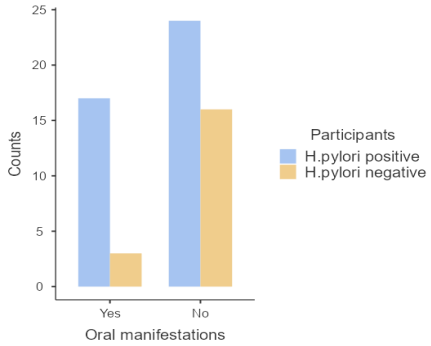


Fig. (1): GIT symptoms among participants. **Fig. (2): Oral manifestations among participants**

Upon analysis of the severity of COVID-19 infection among H.P. +ve and –ve students, there was statistically significant correlation (p=0.027) in which 100% of severe, 77.4% of moderate and 50% of mild cases were H.P. +ve as shown **in table (2) and figure (3).**

Table (2): Severity of corona virus in relation to HP

Severity of corona virus	H.Pylori (+ve)	H.Pylori (-ve)	Total	P-value*
Mild	12 (50%)	12 (50 %)	24(100 %)	**0.027**
Moderate	24 (77.4%)	7 (22.6 %)	31(100 %)	
Severe	5 (100%)	0 (0 %)	5(100 %)	
Total	41 (68.3 %)	19 (31.7 %)	60 (100 %)	

*Chi-square test

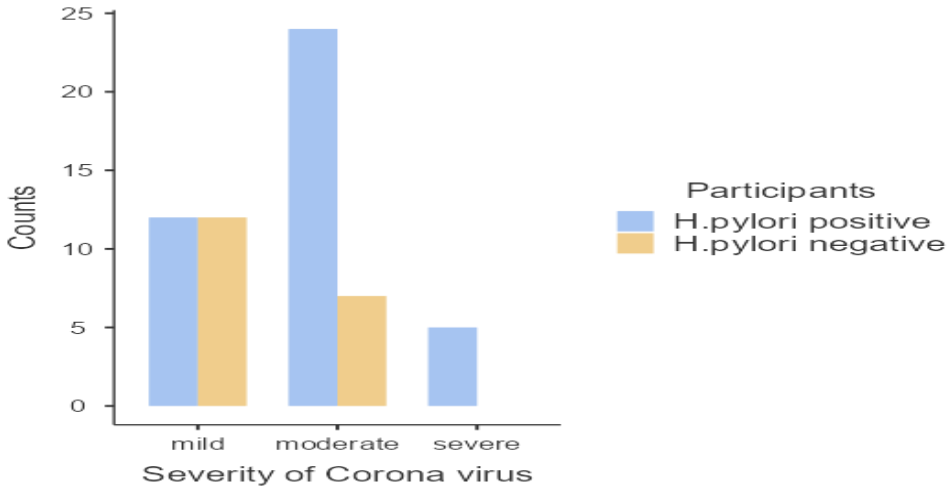


Fig. (3): Severity of corona virus in relation to H.P

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Furthermore, the occurrence of classical COVID-19 symptoms among H.P. +ve individuals was significantly higher for fever, dry cough, dyspnea and loss of taste/smell sensation than H.P.-ve cases (P=0.022, 0.026, 0.035 and 0.007 respectively) **as shown in table (3).**

Table (3): Correlation between HP and symptoms of corona virus

Symptoms present	H.Pylori (+ve)	H.Pylori (-ve)	Total	P-value*
Fever	28 (80 %)	7 (20 %)	35 (58.3 %)	**0.022**
Dry cough	33 (76.7 %)	10 (23.3%)	43 (71.6 %)	**0.026**
Dyspnea	27 (79.4%)	7 (20.6%)	34 (56.6 %)	**0.035**
Loss of taste/smell	26 (83.9 %)	5 (16.1 %)	31 (51.6 %)	**0.007**

*Chi-square test

DISCUSSION

In recent years, the COVID-19 pandemic has been the most important public health problem with a wide range of clinical outcomes, course and severity that vary from mild flu-like symptoms such as; fever, malaise and respiratory symptoms to being fatal within 2-3 weeks from the onset of symptoms. Among the reported symptoms, GIT symptoms including abdominal pain, diarrhea and vomiting were also common. However, the exact mechanism of these symptoms is not entirely comprehended (19, 20).

It is noteworthy, that the main receptors for COVID-19 virus on human cell are the ACE-2 receptors which are abundantly expressed on GIT cells. Thus, it has been postulated that GIT could act as a replication site for COVID-19 (21, 22).

Interestingly, H.P. infection is particularly relevant as it results in migration of intestine specific cell types with a high burden of IM. Consequently, it increases the expression of ACE-2 receptors in the intestine available for COVID-19 binding and cell entry (18, 23). Moreover, IM of gastric mucosa elevates PH of intragastric juice, therefore, decreases inactivation of the SARS-COV-2 virus by gastric acidity (24, 25).

In this context, an emerging body of evidence suggests H.P. infection can increase the susceptibility to COVID-19 and more severe forms of the disease. In particular, the chronic inflammatory state triggered by H.P. infection is important in the course of COVID-19 infection. It is worth noting that H.P. can colonize the oral cavity, hence upper respiratory system colonization, airway inflammation and lung disease (26-31)

Additionally, some researches revealed that H. P. eradication therapy, especially proton pump inhibitors (PPIs) increase the susceptibility to COVID-19 infection. Moreover, recent studies have shown that H.P. infection results in impaired endothelial integrity which is related to poor outcome of COVID-19 infection (28, 32).

Nevertheless, the exact mode of transmission of H.P. remains unclear. The housefly has been suggested as a possible carrier of HP in areas with poor sanitation. Also, oro-fecal and oral-oral routes are possible (20, 33). Despite the fact that many researchers provided evidence for the presence of H.P. infection in dental plaque, saliva, periodontal diseases, apthous stomatitis lesions, burning mouth and halitosis cases, these results remain controversial due to variation in study design, diagnostic methods, inclusion/exclusion criteria and type of control (16).

However, it is obvious that elimination of H.P. from the oral cavity is much more difficult than its eradication from the GIT. Accordingly, it is assumed that the presence of H.P. in dental plaque and saliva as well as its isolation from oral and periodontal lesions may act as a reservoir for the bacterium that may lead to reinfection even after its elimination from GIT (34, 35).

Regarding oral and periodontal diseases, it has been documented that there was an increase in H.P. strains in dental plaque with the development of periodontitis, particularly where periodontal pocket depth of more than 5mm depth are present assuming that subgingival plaque may be regarded as a reservoir for H.P. Furthermore, H.P. has not only been found in patients having recurrent aphthous stomatitis (RAS) but, some studies demonstrated that H.P. eradication therapy resulted in reduction of number and recurrences of RAS (16).

In addition, some researches addressed the correlation of H.P. with a syndrome involving burning, halitosis and lingual dorsum hyperplasia (BHH syndrome) in which they considered H.P. a risk factor for its development and some found that symptoms of BHH disappeared with H.P. eradication therapy (16).

Given the current evidence of the possible relation between H.P. and some oral diseases as well as its correlation with COVID-19 infection, we decided to

conduct the present study to investigate the prevalence of H.P. infection among COVID-19 confirmed dental students in Fayoum University and their association with oral disease.

Some researches revealed that the rapid urease test (RUT) was not sufficiently sensitive for detection of H.P. in the oral cavity, while it has been suggested that H.P. IgG antibodies (ELIZA) have an estimated sensitivity and specificity of 80% and 70% respectively(16, 36). Accordingly, it was the method selected in our study for detection of H.P. positive cases among the study sample.

In the present study which was performed on dental students of Fayoum University in Egypt, participants were selected to be with past history of COVID-19 that was confirmed with RT PCR. According to history taking, most of them were Egyptians and originating from rural area. By detection of H.P. IgG in saliva (using ELISA), our results revealed that the majority of them (68.3%) were H.P. positive. Concerning the incidence and correlation of COVID-19 with H. P. infection, some recent studies have results that are consistent with our findings. Jasmin et al. (20).found that the H. P. infection rate was higher in COVID-19 patients ($p \leq 0.001$) compared to the healthy persons. Furthermore, the coexistence of anti-H.P. IgG and COVID-19 infection were higher in all age groups. In a recent study (37) that used H. P. antibodies rapid test, 83.07% of COVID-19 patients were positive for H.P..

Moreover, our results have shown an evident relation between existence and persistence of GIT symptoms such as nausea, vomiting, diarrhea and abdominal pain and the presence of h.P. infection. These findings were in line with those of Balamtekin et al.(18) in which abdominal pain and diarrhea were strongly correlated with the presence of H P. in COVID-19 patients. They believed that this relationship is attributable to the upregulation of ACE-2 receptors by H.P. infection. Our results were in accordance with Jameel et al. (38) as they suggested that H. P. increases GI symptoms by " over – expression of ACE-2 receptors " in the GIT, thereby causing more virus to enter enterocytes and associated with the severity of infection. In another recent study (37), HP was also regarded as a risk factor for GIT symptoms with COVID-19 infection.

Furthermore, our findings could align with the notion that GIT might act as a replication site for COVID-19 via upregulation of ACE-2 receptors by H.P. infection. This was revealed by the correlation between h.P. infection and classic symptoms of COVID-19 as well as the severity of the disease. These results were in contrast to those of Balamtekin et al. (18) who found no statistically significantly association between the presence of H P. and the clinical severity of the COVID-19,

Based on the available data, only few studies have addressed the relation of H.P. infection and the presence of oral manifestations such as; oral dryness, oral ulceration, symptoms of gingival and periodontal diseases and halitosis. Intriguingly, as we found correlation between COVID-19 and H.P. infection, we have also found significant correlation between H.P. infection and the presences of oral symptoms.

According to the aforementioned data, it seems that H.P. infection represents a risk factor affecting the course and outcome of COVID-19 infection with possible association with oral manifestations.

Declaration of Interests

The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscriptt.

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