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Helicobacter pylori infection and gastric cancer precursor lesions: prevalence and associated factors in a reference laboratory in Southeastern Brazil

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ABSTRACT – **Background** – *Helicobacter pylori* infection is the most important risk factor for gastric atrophy and intestinal metaplasia, both considered gastric cancer precursor lesions. Therefore, the investigation of the occurrence of *H. pylori* infection, precursor lesions and associated factors guides the adoption of specific strategies for the control this type of cancer. **Objective** – To evaluate the prevalence of *H. pylori* infection in patients undergoing upper digestive endoscopy, as well as the prevalence of intestinal metaplasia, atrophy and chronic inflammation and their association with *H. pylori* infection. **Methods** – A retrospective study was performed based on reports of gastric endoscopic biopsies performed in a private laboratory affiliated to the Brazilian Public Health System (SUS). Patients were evaluated for age, gender and type of health service. The samples were evaluated for the presence of *H. pylori*, and also of chronic inflammation, intestinal metaplasia and glandular atrophy. **Results** – Of a total of 4,604 patients (mean age 51±16.6), 63.9% were female and 63.1% coming from private health care service. The prevalence of *H. pylori* infection was 31.7% (n=1,459), and the percentage of infection was significantly higher in patients from public health service (42.0%) in relation to patients from private health service (25.6%). Among *H. pylori* (+) patients, a higher percentage of intestinal metaplasia (17.7% vs 13.3%) and glandular atrophy (17.6% vs 6.9%) were observed when compared to those *H. pylori* (-) (P<0.01). From the patients *H. pylori* (+) with at least one type of precursor lesion (n=418), 161 (38.5%) had metaplasia and chronic inflammation, 160 (38.3%) had atrophy and chronic inflammation and finally 97 (23.2%) presented metaplasia, atrophy and chronic inflammation simultaneously. **Conclusion** – The present study reinforces the association of *H. pylori* infection with gastric cancer precursor lesions in a Brazilian population, emphasizing the importance of infection prevention measures, as well as the treatment of infected patients, especially in regions with lower socioeconomic levels that show a higher prevalence of infection by *H. pylori*.

HEADINGS – *Helicobacter pylori*. Stomach neoplasms. Metaplasia. Atrophic gastritis.

INTRODUCTION

Each year thousands of people seek for specialized assistance due to gastric desorders. The upper digestive endoscopy is the complementary test most widely used to investigate the gastric complaints since, besides allowing an evaluation regarding the existance of inflammation and tumor signs, it also allows to obtain samples of the gastric mucosa for histopathologic evaluation and ethiologic factor investigation. The gastritis stands out among all possible diagnosed pathologies through this procedure[1-3].

The word gastritis is generically defined as being an acute or chronic inflammatory process of the gastric mucosa[4]. The chronic gastritis is a pathology of great importance not only because of its morbidity, but mainly because of the aspects related to its evolution and relationship with gastric cancer[3,5]. Although, gastritis can be caused by several factors, infectious or non-infectious, the most common ethiologic agent linked to the chronic gastritis is the *Helicobacter pylori*[6].

The *H. pylori* is a spiral and flagellated gram-negative bacillus which colonizes preferably the non-acid secretory gastric mucosa such as antrum and cardia, although it can also be found in the oxyntic mucosa found mainly on the fundus and in the gastric body. This bacterium synthetizes several enzymes such as proteases and phospholipases which degrade the mucus layer that protects the gastric epithelium. It also produces the urease which unfolds the urea found in the gastric juice into ammonia and carbon dioxide, neutralizing the gastric pH around the bacterium making it resistant and able to survive in the acid conditions of the stomach. Through its motility, the pathogen colonizes the gastric mucosa, sticking to the mucus producing cells in the stomach, then starting a local inflammation process and the production of toxins which are mostly responsible for the reduction of the mucosa integrity[7-9].

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The *H. pylori* infection leads invariably to a chronic inflammatory process in the stomach which is characterized by an increase in the number of lymphocytes, macrophages and plasmocytes in the lamina propria in variable degrees, that can be accompanied by neutrophils which indicate inflammatory activity[1,5]. This infection when not treated remain for an indefinite time, and is rarely eliminated in a spontaneous way[1,10].

The maintainance of the chronic inflammation induced by the *H. pylori*, besides damaging the cells can, according to the Correa model, trigger a multistage process of carcinogenesis in which the non-atrophic chronic gastritis would evolve to atrophic gastritis (loss of gastrict glands), intestinal metaplasia (replacement for intestinal-type epithelium), dysplasia and gastric adenocarcinoma[11]. Therefore, *H. pylori* infection is the most important risk factor for gastric atrophy and intestinal metaplasia and these latter are considered gastric cancer precursor lesions[12].

The majority of gastric cancer cases are intestinal-type adenocarcinoma, located in the antrum and body of the stomach whose development is usually secondary to gastric atrophy and intestinal metaplasia[11-13]. However, the diagnosis of such pathology is often performed late, when treatment can be less effective. Thus, the knowledge of gastric cancer etiopathogenesis and the investigation of risk factors and precursor lesions become relevant to its prevention, early diagnosis, treatment and increase of patients' life expectancy. So the aim of the present study was to evaluate the prevalence of *H. pylori* infection and its associated factors in patients who underwent upper digestive endoscopy and who had gastric biopsy analyzed at a reference laboratory in Juiz de Fora County, Minas Gerais State, as well as the prevalence of precursor histological changes of gastric cancer and their association with *H. pylori* infection.

METHODS

Retrospective study was performed based on gastric endoscopy biopsy data collected between 2015 and 2016 in a private lab also integrated to the Brazilian Public Health System (*Sistema Único de Saúde* – SUS) – according to the approval of the CEP/UFJF Research Ethic Committee through the legal report number 1.402.229. Only patients with simultaneous samples of gastric antrum and body separately and for whom *H. pylori* were investigated by specific staining were included in the study. For patients with more than one endoscopic exam with biopsies, only the samples corresponding to the last exam request were considered. Patients were evaluated for age, sex and type of the health care service (public or private).

The slides were stained by the hematoxylin-eosin (HE) traditional method and the *H. pylori* research was done by the GRAM staining which shows satisfactory sensitivity, specificity, positive predictive value and accuracy for bacillus identification[14]. Samples were evaluated for the presence of *H. pylori* in the antrum and/or gastric body (present or absent) and according to four morphologic variants recommended by the Sydney System: chronic inflammation, inflammatory activity, intestinal metaplasia and glandular atrophy, all these variables classified as absent or present, and when present ranked as mild, moderate and severe[15].

Chronic inflammation was considered when high level of mononuclear leukocytes, including lymphocytes, plasmocyte and macrophages was found. Inflammatory activity was confirmed by the detection of polymorphonuclear (neutrophils) on the lamina propria, epithelium or lumen. Glandular atrophy was characterized by the loss of glands, glandular colon hyperplasia and mucin depletion. With regards to the intestinal metaplasia, it has been detected when the gastric mucosa resembled the intestine mucosa, showing goblet cells with or without gland distortion[12,16,17].

The Excell program was used for data input and data analysis was performed by Stata software version 9.0. Differences in the distribution of the variables were assessed by the chi-square test and those with value $P<0.05$ were considered statistically significant. Odds ratios (OR) and respective 95% confidence intervals (95%C.I.) were calculated for each gastric cancer precursor lesion in relation to the presence of *H. pylori* infection.

RESULTS

A total of 4,604 patients who met the inclusion criteria were evaluated, with a mean age of 51 years (±16.6). The majority of them were women (n=2,941; 63.9%) and coming from the private health care service (n=2,903; 63.1%). As shown in TABLE 1, the prevalence of *H. pylori* infection in the study population was 31.7% (n=1,459). The smallest percentage of infection by *H. pylori* (24.8%) was detected among patients under 30 years of age, while among those ranging between 30–39 years of age, the percentage was the highest (40.6%), and a decrease of infection was detected among patients age 40 and over ($P<0.01$). The frequency of infection was higher among men (33.4%) rather than women (30.7%), however with only marginal significance ($P=0.07$). With regards to the origin of the health care service, the percentage of *H. pylori* infection was significantly higher in patients from public health service (42.0%) when compared with patients from private health service (25.6%) ($P<0.01$).

TABLE 1. Prevalence of *H. pylori* infection according to age, sex and health service. Juiz de Fora/MG, Brazil.

Variable	*H. pylori* negative n (%) 3,145 (68.3%)	*H. pylori* positive n (%) 1,459 (31.7%)	Total	*P*-value
Age				< 0.01
< 30 yrs	422 (75.2%)	139 (24.8%)	561	
30–39 yrs	336 (59.4%)	230 (40.6%x)	566	
40–49 yrs	566 (66.4%)	286 (33.6%)	852	
50–59 yrs	747 (67.1%)	366 (32.9%)	1,113	
≥ 60 yrs	1,074 (71.0%)	438 (29.0%)	1,512	
Sex				0.07
Female	2,037 (69.3%)	904 (30.7%)	2,941	
Male	1,108 (66.6%)	555 (33.4%)	1,663	
Health service				< 0.01
Private	2,159 (74.4%)	744 (25.6%)	2,903	
Public (SUS)	986 (58.0%)	715 (42.0%)	1,701	

When evaluating the prevalence of gastric cancer precursor lesions in the study polulation, 676 (14.7%) patients showed intestinal metaplasia in the body and/or antrum gastric. Among *H. pylori* (+) patients a higher percentage of intestinal metaplasia (17.7%) was detected when compared with *H. pylori* (-) patients (13.3%) ($P<0.01$). The odds ratio for the occurrence of metaplasia

associated with *H. pylori* infection was 1.40 (95% IC: 1.18–1.66) (TABLE 2). Glandular atrophy was detected in 474 (10.3%) of patients. Similarly, the percentage of glandular atrophy was significantly higher between *H. pylori* (+) patients (17.6%) than among *H. pylori* (-) patients (6.9%) (P<0.01). The chance of glandular atrophy occurrence in *H. pylori* (+) was about 3 times higher than in *H. pylori* (-) patients (OR: 2.88; 95% IC: 2.40–3.50) (TABLE 3).

TABLE 2. Prevalence of intestinal metaplasia according to *H. pylori* infection status. Juiz de Fora/MG, Brazil.

Infection status	Intestinal metaplasia* Absent n (%) 3,928 (85.3%)	Present n (%) 676 (14.7%)	Total 4,604	OR	95%CI
H. pylori (-)	2,727 (86.7%)	418 (13.3%)	3,145	1	
H. pylori (+)	1,201 (82.3%)	258 (17.7%)	1,459	1.40	1.18–1.66

*P<0.01; OR: odds ratio; 95%CI: 95% confidence interval.

TABLE 3. Prevalence of glandular atrophy according to *H. pylori* infection status. Juiz de Fora/MG, Brazil.

Infection status	Atrophy* Absent n (%) 4,130 (89.7%)	Present n (%) 474 (10.3%)	Total 4,604	OR	95% CI
H. pylori (-)	2,928 (93.1%)	217 (6.9%)	3,145	1	
H. pylori (+)	1,202 (82.4%)	257 (17.6%)	1,459	2.88	2.40–3.50

*P<0.01; OR: odds ratio; 95%CI: 95% confidence interval.

In addition, the coexistence of gastric cancer precursor lesions with chronic inflammation in *H. pylori* (+) patients was also analyzed (FIGURE 1). It has been observed that among *H. pylori* (+) patients who had at least one type of precursor lesion (n=418), 161 (38.5%) had metaplasia and chronic inflammation, 160 (38.3%) had atrophy and chronic inflammation and finally 97 (23.2%) exhibited metaplasia, atrophy and chronic inflammation simultaneously. It is worthy highlight that the majority of the *H. pylori* (+) patients (n=1,459) showed only chronic inflammation (n=1,041; 71.3%) and no patient showed metaplasia or atrophy alone.

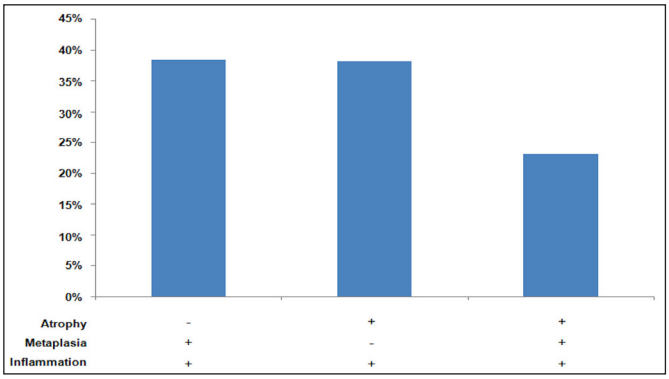

FIGURE 1. Coexistence of intestinal metaplasia, glandular atrophy and chronic inflammation in *H. pylori* positive patients. Juiz de Fora/MG, Brazil.

DISCUSSION

Studies show that *H. pylori* infection is very common, mainly in developing countries, suggesting that about 50% of the world population is infected by this bacterium[18-20]. In meta-analysis study, performed to estimate the worldwide prevalence of the *H. pylori*, it has been observed a prevalence of approximately 71% in Brazil[21]. In the present study, however, we found a prevalence of 31.7% of *H. pylori* infection. This lower prevalence is in agreement with a recent study conducted in Southern Brazil[22] and might be related to the socioeconomic characteristics of the study population which is not representative of the Brazilian population since the majority of the patients investigated came from private health care service (63.1%). Such aspect can reflect a better social-economic level of the study population, and explain, at least in part, the smallest prevalence of the infection since *H. pylori* infection is frequently related to social-economic level of a specific population and it can reach 90% in developing countries and less than 40% in developed countries[21-23]. On the other hand, Brazilian studies included in the meta-analysis were mostly related to populations with lower socioeconomic level, which must have contributed to the highest estimated prevalence in Brazil[21].

Another aspect to be taken into consideration is the fact that the national prevalence estimate of *H. pylori* in the meta-analysis study was obtained from studies in which the diagnosis of the infection was mainly performed by serology tests[21] while in the present study the diagnosis was performed by the standard histology method with specific staining. Serological method is mainly based on detecting IgG antibodies and can be influenced by geographic variations and characteristics of the studied populations, and local validation of this test is often necessary in order to make adjustments in the cut off levels for specific populations[23,24]. Another disadvantage lies on the fact that this method can be influenced by prolonged maintenance of antibodies in the host even after the elimination of the infection[25]. In addition, the accuracy of the serological tests depends on the antigen used in the commercial kit and the prevalence of specific strains varies significantly in different regions[23]. The histological method, used in the current study, allows the visualization of the pathogen and it also enables to assess changes in the gastric mucosa, although it is an invasive method, presenting sensibility and specificity ranging from 53% to 93% depending on the representativeness of the sample, the colonization density and the pathologist's experience[23,24]. Therefore, the advantages and disadvantages of the different diagnosis methods used to estimate the prevalence of *H. pylori* should be taken into account when comparing results between studies.

H. pylori is a resistant bacterium that can remain viable for long periods of time in the environment. It has already been isolated in vegetables, milk, water and droppings[26,27]. The transmission among human usually occurs by oral-oral and fecal-oral vias, with a higher prevalence rate in lower income populations where the contamination is related to precarious conditions of housing, dietary habits and hygiene as well as bad sanitation conditions including lack of appropriate sewage system and treated water[21,23,26]. This relation was corroborated in this current study since a significantly higher percentage of *H. pylori* infection was observed in patients from the public health service (SUS) (42%) which probably had a lower socioeconomic condition compared to patients from the private health service (25.6%). In this scenario, the improvement of sanitary conditions could contribute for reducing *H. pylori*

prevalence among vulnerable populations given that the reduction in the incidence and prevalence of *H. pylori* observed in the past decades has been related to industrialization and improvement of sanitary and social-economic conditions in different countries[22,26].

The prevention of *H. pylori* infection becomes essential not only due to morbidity linked to the disease but also by the fact that *H. pylori* is considered an important risk factor for atrophy and intestinal metaplasia, both classified as gastric cancer precursor lesions[12,28]. In this context, the prevalence of atrophy and intestinal metaplasia correlates positively with the frequency of gastric carcinoma in populations from certain countries[2,29,30].

The prevalence of atrophy and intestinal metaplasia in general population was widely analyzed through a systematic review and meta-analysis published in 2014, which included 107 original studies comparing countries with low to moderate versus high incidence of gastric cancer[30]. In this review, the prevalence of atrophy in the general population was 33% (26%–41%), while intestinal metaplasia was 25% (19%–30%). In countries with high incidence of gastric cancer, the prevalence of atrophy was significantly higher (41.7%) than in countries with low to moderate incidence (22.8%). Nevertheless, intestinal metaplasia did not differ significantly between these countries, ranging from 21.7% in countries with low to moderate incidence of gastric cancer to 28.1% in countries with high incidence. In the current study, the prevalence of atrophy and metaplasia in patients was 10.3% and 14.7% respectively, which is lower than expected for countries with low incidence of gastric cancer. However, both prevalence follow the same tendency observed in some studies so far performed in Brazil in order to estimate the prevalence of gastric cancer precursor lesions. Muller et al. found prevalence of 3% for atrophy and 15% for metaplasia in dyspeptic patients from the South region of Brazil[31]. Motta et al. detected prevalences of 11.2% and 21.6% for atrophy and metaplasia respectively in patients from the Brazilian Northeast region[32].

When the prevalence of precursor lesions were evaluated in relation to *H. pylori* infection, we found that both atrophy and metaplasia were significantly more frequent in *H. pylori* (+) patients rather than in *H. pylori* (-), suggesting the presence of bacteria as a risk factor for these lesions. In the presence of *H. pylori*, the prevalence of atrophy was 2.5 times higher (17.6 vs 6.9%) and metaplasia was 1.3 times higher (17.7 vs 13.3%) compared to *H. pylori* (-) patients. These results are in accordance with several studies[16,33-35] and also with the findings of the meta-analysis mentioned above in which the prevalence of the atrophy was 2.7 times higher and metaplasia was 2.1 times higher in individuals infected by *H. pylori* than in uninfected individuals[30]. In the current study the percentage difference between *H. pylori* (+) and *H. pylori* (-) patients was higher in atrophy than in metaplasia. In this context, it is noteworthy that although *H. pylori* represents a risk factor for both atrophy and metaplasia, bacterial factors seem to exert a higher influence on the atrophy, whereas environmental and host factors would also play an important role in the development of metaplasia[36], which could explain, at least in part, the smaller percentage difference of metaplasia between individuals infected or not by *H. pylori*.

Atrophy and metaplasia are widely recognized as precursor lesions of intestinal-type gastric cancer, however it is important to highlight that the presence of these lesions does not always lead to the development of cancer[28,37-39]. Moreover, intestinal metaplasia does not necessarily arise only after atrophy, replacing the loss of parietal cells. It can, many times, inversely appear in the non-atrophic mucosa resulting in focal atrophy or it can even appear in response to different aggressions to the gastric mucosa[40]. Regardless of the order in which these lesions appear, inflammation is seen as the main driver of these pathological changes that can trigger the carcinogenic cascade suggested by Correa (1988)[11-13,41,42]. In this scenario, several mechanisms through which the inflammation could promote the development of gastric cancer should be considered, including the induction of the cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) pathway and the activation of NF-KB and Stat3, as well as the activation of the signalingviaTLR/MyD88[43-46]. In addition, several virulence factors present in *H. pylori,* such as CagA protein and peptideogly may play a crucial role in the gastric inflammation[46,47].

Given the importance of inflammation in the gastric carcinogenesis process, we also evaluated the coexistence of atrophy and/or metaplasia with the chronic inflammation in *H. pylori* (+) patients, since the atrophy in association with chronic inflammation can result in the development of a more proliferating metaplasia which would favor the development of dysplasia and the evolution to cancer[13,48]. It was observed that among *H. pylori* (+) patients that had some type of precursor lesion, all had associated chronic inflammation: 38.5% with atrophy, 38.3% with metaplasia, and 23.2% had atrophy, metaplasia and chronic inflammation simultaneously, highlighting the importance of *H. pylori* eradication in order to control the inflammation in these patients.

Although the eradication of *H. pylori* does not necessarily result in complete regression of metaplasia and atrophy, it can retard the development or diminish the severity of these lesions[28,42,49]. In addition, it reduces significantly or interrupts the evolution of the inflammation of the gastric mucosa and leads to normalization of changes that can cause mutation of mucosa cells, so reducing the risk of gastric cancer[23,40,50]. Studies in animal models of gastric cancer showed that the eradication of *H. pylori* resulted in regression of the gastric inflammation with reduced levels of proinflammatory cytokines as well as reduction of epithelial cells proliferation and restoration of the normal architecture, contributing to a lower dysplasia and reduction of gastric cancer risk specially when treatment was performed in the early stage of *H. pylori* infection[51,52]. Such findings strengthen the need for follow ups and treatment of patients infected by *H. pylori*, especially those with concomitant inflammation and gastric cancer precursor lesions.

CONCLUSION

The present study contributes to a better understanding regarding *H. pylori* infection and associated factors in a Brazilian population, and points to the association of this infection with gastric cancer precursor lesions, reinforcing the importance of prevention measures to avoid the infection as well as in order to favor the treatment for infected patients, mainly among regions with lower socioeconomic levels that tend to show higher prevalence of *H. pylori* infection.

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Authors' contribution

Rodrigues MF: planning of the study; literature research, analysis and interpretation of data, writing and revision of the manuscript. Guerra MR: statistical analysis, data interpretation, critical revision of manuscript. Alvarenga AVR: literature research, data collection, data interpretation, text writing. Souza DZO: literature research, data collection. Costa RAVS: data collection. Cupolilo SMN: conception and design of the study, data interpretation, critical revision of manuscript.

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RESUMO – **Contexto** – A infecção por *Helicobacter pylori* é o fator de risco mais importante para atrofia gástrica e metaplasia intestinal, ambas consideradas lesões precursoras do câncer gástrico. Portanto, a investigação da ocorrência de infecção por *H. pylori*, das lesões precursoras e dos fatores associados orienta a adoção de estratégias específicas para o controle deste tipo de câncer. **Objetivo** – Avaliar a prevalência de infecção por *H. pylori* em pacientes submetidos à endoscopia digestiva alta, bem como a prevalência de metaplasia intestinal, atrofia e inflamação crônica e a associação destas com a infecção por *H. pylori*. **Métodos** – Foi realizado um estudo retrospectivo com base em laudos de biópsias endoscópicas gástricas realizadas em laboratório privado afiliado ao Sistema Único de Saúde (SUS). Os pacientes foram avaliados quanto à idade, sexo e tipo de serviço de saúde. As amostras foram avaliadas quanto à presença de *H. pylori* e também de inflamação crônica, metaplasia intestinal e atrofia glandular. **Resultados** – Do total de 4.604 pacientes (idade média de 51±16,6), 63,9% eram do sexo feminino e 63,1% provenientes de serviços de saúde privado. A prevalência de infecção por *H. pylori* foi de 31,7% (n=1.459) e o percentual de infecção foi significativamente maior nos pacientes do serviço público de saúde (42,0%) em relação aos pacientes do serviço privado de saúde (25,6%). Entre os pacientes com *H. pylori* (+), foi observado maior percentual de metaplasia intestinal (17,7% vs 13,3%) e atrofia glandular (17,6% vs 6,9%) quando comparados aos *H. pylori* (-) (P<0,01). Dos pacientes *H. pylori* (+) com pelo menos um tipo de lesão precursora (n=418), 161 (38,5%) apresentaram metaplasia e inflamação crônica, 160 (38,3%) apresentaram atrofia e inflamação crônica e, finalmente, 97 (23,2%) apresentaram metaplasia, atrofia e inflamação crônica simultaneamente. **Conclusão** – O presente estudo reforça a associação da infecção por *H. pylori* com lesões precursoras de câncer gástrico em uma população brasileira, enfatizando a importância de medidas de prevenção de infecção, bem como o tratamento de pacientes infectados, principalmente em regiões com níveis socioeconômicos mais baixos que apresentam maior prevalência de infecção por *H. pylori*.

DESCRITORES – *Helicobacter pylori*. Neoplasias gástricas. Metaplasia. Gastrite atrófica.

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