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An investigation into the relationship between anti-*Helicobacter pylori* and anti-*Saccharomyces cerevisiae* antibodies in patients with axial spondyloarthritis and Crohn disease

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Abstract Spondyloarthritis (SpA) is a musculoskeletal inflammatory disease linked with immune responses to intestinal microbiota, and subclinical intestinal ulcerations that are closely related to inflammatory bowel diseases. *Helicobacter pylori* is a common cause of gastroduodenal ulceration, and anti-*Saccharomyces cerevisiae* antibodies (ASCA) are associated with intestinal inflammation in both Crohn disease (CD) and SpA. We investigated the relationship between *H. pylori* and ASCA. Ninety-one patients with axial SpA and forty with CD were included. ASCA IgG/IgA and anti-*H. pylori* IgG titers were assessed by ELISA. The proportion of ASCA+ patients in the positive and negative anti-*H. pylori* IgG groups with SpA and CD were compared using Chi-square tests, and correlations were evaluated using the Spearman's coefficient. Anti-*H. pylori* IgG titers were significantly negatively correlated with the ASCA IgG ($r = -0.563$, $p < 0.001$) and IgA ($r = -0.342$, $p = 0.019$) titers in the axial SpA patients. The same pattern of negative correlation was also observed in the CD patients. Anti-*H. pylori*+ serology was significantly more frequent in axial SpA patients than in those with CD (52.4 vs. 18.4 %, $p < 0.001$), while ASCA+ serology was significantly more frequent in CD patients than in SpA patients. A negative correlation between the anti-*H. pylori* titers and ASCA was found for axial SpA and CD. Anti-*H. pylori*+ serology was more frequent in SpA than in CD, while ASCA positivity was more frequent in CD patients than in those with SpA. A possible influence of *H. pylori* on the development of ASCA needs further investigation.

Keywords *Helicobacter pylori* · *Saccharomyces cerevisiae* · Spondyloarthritis · Ankylosing spondylitis · Crohn disease · Inflammatory bowel disease

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Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease that primarily affects the axial skeleton, leading to structural damage and a loss of joint function. Subtypes of SpA include ankylosing spondylitis (AS), the most common and representative form; reactive arthritis (ReA); arthritis in patients with inflammatory bowel disease (IBD), as either Crohn disease (CD) or ulcerative colitis; and psoriatic arthritis [1–3].

A link between IBD and SpA has largely been recognized. They share common genetic backgrounds; the first-degree relatives of patients with AS have a threefold greater risk of IBD than unrelated controls matched for age and sex [4], and many similar susceptibility loci have been described between IBD and AS [5]. There is a significant overlap in the clinical manifestations of IBD and SpA; the cumulative incidence of all forms of SpA increases to approximately 19 % by 30 years post-diagnosis of CD [6]. However, this percentage of clinical overlap is probably only the visible evidence of a more important underlying connection. More than 60 % of patients with AS without intestinal clinical symptoms have microscopic signs of intestinal inflammation [7]. In addition, the presence of subclinical intestinal inflammation in other subtypes of SpA has been corroborated by many investigators [8–11].

Other evidence for the link between IBD and SpA is provided by anti-*Saccharomyces cerevisiae* antibodies (ASCA). These antibodies were initially described in patients with CD [12], occurring in up to 69 % of patients [13], but are not specific for this disease. ASCA are also observed in approximately 20 % of patients with SpA [14, 15]. In addition to other antibodies against epitopes from intestinal microorganisms, such as *Escherichia coli* outer membrane porin C (anti-OmpC), ASCA are markers of more severe intestinal disease in patients with CD. These antibodies are associated with fistulizing, structuring, and perforating disease, and patients with ASCA at the time of diagnosis for CD are more likely to require surgery [13, 16].

The factors that lead a patient with SpA to develop significant intestinal disease are not understood. However, the appearance of antibodies against elements of the intestinal microbiome (e.g., ASCA, anti-OmpC) suggests a role for a loss of tolerance to this microbiome. *Helicobacter pylori* is an important element in the human gastrointestinal microbiome. Initial gastroduodenal infection with *H. pylori* typically occurs during childhood after oral intake and the bacteria tend to remain in the host unless treated [17–19]. *H. pylori* is one of the most common infections worldwide, and the prevalence of infection among adults is more than 80 % in many developing countries, as compared with 20–50 % in developed nations, probably due to better hygienic conditions [17, 18]. *H. pylori* infection causes chronic gastritis and peptic ulcer disease [20], and it increases gastrointestinal permeability, which returns to a normal level after eradication of the infection [21].

The relationship between the presence of *H. pylori* and the emergence of ASCA has not yet been investigated. Theoretically, by increasing gastrointestinal permeability, *H. pylori* infection could be a facilitator to the development of ASCA. However, previous studies have demonstrated that the frequency of anti-*H. pylori* antibodies is actually lower in patients with IBD than in healthy controls, and a protective role for *H. pylori* against the development of IBD has been proposed [22, 23]. From this perspective, a negative relationship between *H. pylori* and ASCA would be expected.

The goal of this study was to investigate whether there is a relationship between infection by *H. pylori* and ASCA positivity in patients with SpA. The primary objective was to determine the frequency of ASCA positive (ASCA+) serology in patients with axial SpA relative to their anti-*H. pylori* IgG serological status, that is, anti-*H. pylori* IgG positive (anti-*H. pylori* IgG+) versus anti-*H. pylori* IgG negative (anti-*H. pylori* IgG−), and to correlate the ASCA titers with the anti-*H. pylori* IgG titers in axial SpA patients. For comparative purpose, the relationship between ASCA and *H. pylori* serology was also studied in a sample of CD patients. The secondary objective of this study was to determine the frequency of clinical manifestations of axial SpA with respect to anti-*H. pylori* IgG serostatus.

Methods

Study design and population

We conducted a cross-sectional study from January 2012 to November 2012 with a consecutive sampling of patients with axial SpA—as defined by the classification criteria for axial SpA established by the Assessment of SpondyloArthritis international Society (ASAS) [24]—who were followed at the rheumatology outpatient clinic of the University Hospital. The patients with a diagnosis of ReA, which was defined by a history of urethritis or diarrheal illness before the onset of articular manifestations, and patients with a diagnosis of IBD, celiac disease, or unexplained symptoms from the gastrointestinal tract were excluded from the axial SpA group. These criteria were intended to exclude patients with other known ASCA-related intestinal disease (IBD and celiac disease) and patients with SpA due to a known bacterial trigger (ReA).

To calculate the required sample size, we considered the hypothesis that among patients with axial SpA, the frequency of ASCA+ serology is not equal in the positive and negative anti-*H. pylori* IgG groups. In a study conducted by Aydin et al. [15], the prevalence of ASCA+ serology was 20 % among patients with SpA. Thus, to calculate the required sample size, we estimated that the frequency of ASCA+ serology in one of the SpA groups defined by *H. pylori* serology would be at least 30 % and in the other group, the frequency of ASCA+ serology would be similar to that of healthy individuals (usually less than 5 %). To reach a significance level of 95 % ($p < 0.05$) with a statistical power of 80 %, 33 patients were required in each group

to determine whether the presence of anti-*H. pylori* IgG+ serology modifies the frequency for the ASCA+ serology in 30 % from baseline.

We also included a sample of consecutive patients with CD to assess the relationship between anti-*H. pylori* serology and ASCA in these patients, which were diagnosed with biopsies obtained by colonoscopy. The CD patients with axial musculoskeletal involvement, as defined by the ASAS criteria [24] were excluded from this group.

Data collection

The axial SpA patients included in the study were interviewed by the researchers, and their charts were reviewed to determine their demographic and clinical characteristics. The criteria used to identify peripheral arthritis were a history of or evidence in a physical examination of joint pain and edema in the knees, ankles, elbows, hands, or feet. Extra-articular manifestations of uveitis, defined by the presence of a typical history of recurrent painful red eye or an ophthalmologic diagnosis of uveitis, and cutaneous disease, defined by a history or physical evidence of psoriatic rash, were also assessed. Portuguese adaptations of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), and the Bath Ankylosing Spondylitis Metrology Index (BASMI) were utilized for the disease assessment of the axial SpA patients [25]. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated as previously defined using C-reactive protein as the laboratory variable [26]. A previous history of treatment for *H. pylori* eradication was also assessed.

Laboratory tests

Blood samples were collected from the axial SpA and CD patients by venipuncture and centrifuged to separate the serum, which was frozen at −20 °C until enzyme-linked immunosorbent assays (ELISA) were performed using the following kits: Ridascreen™ ELISA for anti-*H. pylori* IgG (R-Biopharm AG, Darmstadt, Germany), with a reference value of 16 U/mL (<10 U/mL negative; 10–16 U/mL indeterminate; ≥16 U/mL positive), intra-assay reproducibility of 3.0–4.8 % and inter-assay reproducibility of 4.4–9.9 %; and ORG 545 ELISA for ASCA IgG/IgA (Orgentec Diagnostika GmbH, Mainz, Germany) with a reference value of 10U/mL (<10 U/mL negative, ≥10 U/mL positive), intra-assay reproducibility of 4.3–8.8 %,and inter-assay reproducibility of 3.8–7.5 %.

Statistics

Patients with indeterminate titers of anti-*H. pylori* IgG (10–16 U/mL) were excluded from the analyses that compared the proportion of patients with ASCA+ serology and the frequency of clinical manifestations between the positive and negative anti-*H. pylori* IgG groups. For these analyses, we used the Chi-square test or Fisher exact test as indicated. Due to the normal distribution of results as determined with a Kolmogorov–Smirnov test, a Student's *t* test was used to compare the BASDAI, BASFI, BASMI, and ASDAS results between the positive and negative anti-*H. pylori* IgG groups.

To correlate the anti-*H. pylori* IgG titers with the ASCA titers, patients with negative results for both tests were excluded from the analysis. Due to the non-parametric distribution of these results, the Spearman's coefficient was used. All tests were two-tailed, and all analyses were performed using SPSS™ 17.0 for Windows® (SPSS Inc., Chicago, IL, USA).

Ethics

Ethical approval was obtained from the Ethical Committee on Human Research at UFSC (protocol 2395). The research protocol conformed to the provisions of the World Medical Association's Declaration of Helsinki. All subjects provided written informed consent before inclusion in the study, and patient anonymity was preserved.

Results

Of 93 axial SpA patients who were initially eligible, 2 patients refused to participate and were excluded from the study. There were no previously diagnosed cases of ReA, IBD, or celiac disease, and 91 axial SpA patients were enrolled in and completed the study. Of these, 43 patients were anti-*H. pylori* IgG+ (>16 U/mL), and 39 patients were anti-*H. pylori* IgG− (<10 U/mL); 9 patients had indeterminate titers (10–16 U/mL). The baseline demographic and clinical characteristics of the 82 SpA patients with positive and negative anti-*H. pylori* IgG serology are presented in Table 1. Also shown, with respect to the anti-*H. pylori* IgG serostatus, are the results obtained for the frequency of ASCA+ serology, the presence of peripheral arthritis and extra-articular manifestations of SpA, and the BASDAI, BASFI, BASMI, and ASDAS scores. The data indicated there was a lower frequency of ASCA+ serology in the anti-*H. pylori* IgG+ group than in the anti-*H. pylori* IgG- group (20.9 vs. 33.3 %), but this difference was not statistically significant ($p = 0.224$). The frequency of peripheral arthritis, extra-articular manifestations, and the BASDAI, BASFI, BASMI, and ASDAS scores were similar between the two groups.

Forty patients with biopsy-proven CD without axial musculoskeletal involvement were included as a comparison

Table 1 Distribution of demographic and clinical features, ASCA positivity and disease scores in axial SpA and CD patients according anti-*H. pylori* positive versus negative serostatus

Axial SpA, *n*	Anti-*H. pylori* IgG			*p*
	Positive	Negative	Total	
	43	39	82	
Age, years ± SD	44.6 ± 12.5	41.7 ± 11.9	43.2 ± 12.2	0.288
Male gender, *n* (% in *H. pylori* serostatus group)	35 (81.4 %)	27 (69.2 %)	62 (75.6 %)	0.200
BMI, Kg/m^2 ± SD	26.9 ± 5.0	26.1 ± 3.0	26.6 ± 4.2	0.430
Time since diagnosis, years ± SD	9.1 ± 6.8	8.7 ± 6.3	8.9 ± 6.5	0.804
Anti-TNF agent, *n* (% in *H. pylori* serostatus group)	26 (60.5 %)	26 (66.7 %)	52 (63.4 %)	0.560
DMARD, *n* (% in *H. pylori* serostatus group)	8 (18.6 %)	6 (15.4 %)	14 (17.1 %)	0.699
NSAID, *n* (% in *H. pylori* serostatus group)	21 (48.8 %)	16 (41.0 %)	37 (45.1 %)	0.478
Corticosteroids, *n* (% in *H. pylori* serostatus group)	6 (14.0 %)	5 (12.8 %)	11 (13.4 %)	1.000
H. pylori treatment	1 (2.3 %)	4 (10.3 %)	5 (6.1 %)	0.186
ASCA IgG +, *n* (% in *H. pylori* serostatus group)	9 (20.9 %)	13 (33.3 %)	22 (26.8 %)	0.224
ASCA IgA +, *n* (% in *H. pylori* serostatus group)	1 (2.3 %)	3 (7.7 %)	4 (4.9 %)	0.342
Peripheral arthritis, *n* (% in *H. pylori* serostatus group)	29 (67.4 %)	25 (64.1 %)	54 (65.9 %)	0.750
Uveitis, *n* (% in *H. pylori* serostatus group)	24 (55.8 %)	20 (51.3 %)	44 (53.7 %)	0.681
Psoriatic rash, *n* (% in *H. pylori* serostatus group)	9 (20.9 %)	11 (28.2 %)	20 (24.4 %)	0.444
BASDAI, mean ± SD	4.4 ± 2.8	4.2 ± 3.0	4.3 ± 2.9	0.775
BASFI, mean ± SD	4.1 ± 2.5	4.7 ± 3.0	4.4 ± 2.8	0.310
BASMI, mean ± SD	2.8 ± 2.3	3.1 ± 2.5	3.0 ± 2.4	0.570
ASDAS, mean ± SD	3.7 ± 1.3	3.7 ± 1.4	3.7 ± 1.3	0.931
Crohn disease, *n*	Anti-*H. pylori* IgG			*p*
	Positive	Negative	Total	
	7	31	38	
Age, years ± SD	44.4 ± 13.8	36.0 ± 12.6	38.2 ± 13.9	0.123
Male gender, *n* (% in *H. pylori* serostatus group)	1 (14.3 %)	11 (35.5 %)	12 (31.6 %)	0.395
Anti-TNF agent, *n* (% in *H. pylori* serostatus group)	4 (57.1 %)	18 (58.1 %)	22 (57.9 %)	1.000
Immunosuppressants *n* (% in *H. pylori* serostatus group)	3 (42.9 %)	13 (41.9 %)	16 (42.1 %)	1.000
	Positive ($n = 7$)	Negative ($n = 30$)	Total ($n = 37$)	
ASCA IgG+, *n* (% in *H. pylori* serostatus group)	3 (42.9 %)	19 (63.3 %)	22 (59.5 %)	0.408
ASCA IgA+, *n* (% in *H. pylori* serostatus group)	2 (28.6 %)	14 (46.7 %)	16 (43.2 %)	0.674

SpA spondyloarthritis, *CD* Crohn disease, *H. pylori Helicobacter pylori, ASCA* anti-*Saccharomyces cerevisae* antibodies, *BMI* body mass index, *TNF* tumor necrosis factor, *DMARD* disease-modifying anti-rheumatic drug, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *ASDAS* ankylosing spondylitis disease activity score, *Immunossupr.* azathioprine or mesalazine

group. Of these, 7 were anti-*H. pylori* IgG+ and 31 were anti-*H. pylori* IgG−. Two had indeterminate anti-*H. pylori* titers. Table 1 also presents the baseline demographic characteristics and frequency of ASCA+ serology in the 38 CD patients with positive versus negative anti-*H. pylori* IgG serology. One CD patient was missed during the ASCA serology testing. As in the axial SpA patients, although a lower frequency of ASCA+ serology was observed in the anti-*H. pylori*+ group, statistical significance was not reached.

The proportion of anti-*H. pylori* IgG+ patients in the CD group was significantly lower than that in the axial SpA group. Conversely, the proportions of ASCA IgG+ and ASCA IgA+ were significantly higher in the CD group than in the axial SpA group. These results are presented in Table 2.

Figure 1a shows a graph of the correlation between the ASCA IgG and anti-*H. pylori* IgG titers in the axial SpA patients. For this analysis, patients with negative serologic tests for both antibodies were excluded. Among the remaining 58 patients, we observed a significant negative correlation between the ASCA and anti-*H. pylori* IgG titers ($r = -0.563$, $p < 0.001$). Figure 1b shows a graph of the correlation between the ASCA IgA and anti-*H. pylori* IgG titers in the axial SpA patients. Patients negative for both serologic tests were also excluded from this analysis.

Table 2 Proportion of anti-*H. pylori* IgG, ASCA IgG and ASCA IgA positive or negative serostatus according diagnosis (axial SpA vs. CD)

Group	Anti-*H. pylori* IgG		
	Positive	Negative	Total
Axial SpA	43 (52.4 %)	39 (47.6 %)	82 (100 %)
CD	7 (18.4 %)	31 (81.6 %)	38 (100 %)
	***p* < 0.001**		
	ASCA IgG		
	Positive	Negative	Total
Axial SpA	22 (26.8 %)	60 (73.2 %)	82 (100 %)
CD	22 (59.5 %)	15 (40.5 %)	37 (100 %)
	***p* = 0.001**		
	ASCA IgA		
	Positive	Negative	Total
Axial SpA	4 (4.9 %)	78 (95.1 %)	82 (100 %)
CD	16 (43.2 %)	21 (56.8 %)	37 (100 %)
	***p* < 0.001**		

H. pylori Helicobacter pylori, *ASCA* anti-*Saccharomyces cerevisae* antibodies, *SpA* spondyloarthritis, *CD* Crohn disease

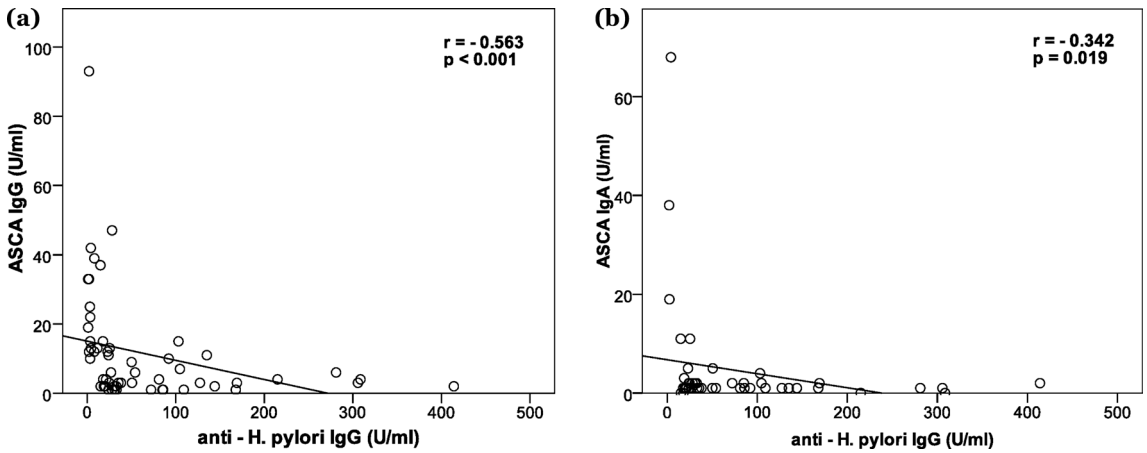

Fig. 1 **a** Correlation between ASCA IgG and anti-*H. pylori* IgG titers in axial spondyloarthritis patients in which at least one of these tests was positive ($n = 58$). **b** Correlation between ASCA IGA and anti-*H. pylori* IgG titers in axial spondyloarthritis patients in which at least one of these tests was positive ($n = 47$). *H. pylori*, *Helicobacter pylori*; ASCA, anti-*Saccharomyces cerevisiae* antibodies

Among the remaining 47 patients, a significant negative correlation was also observed between the ASCA IgA and anti- *H. pylori* IgG titers ($r = -0.342$, $p = 0.019$).

Figure 2a shows a graph of the correlation between the ASCA and anti-*H. pylori* IgG titers in CD patients, with the patients negative for both serologic tests excluded. A significant negative correlation was found between the ASCA IgG and anti-*H. pylori* IgG titers ($r = -0.527$, $p = 0.003$) in the 29 seropositive patients. Similarly, Fig. 2b shows a graph of the correlation between the ASCA IgA and anti-*H. pylori* IgG titers in the seropositive CD patients ($n = 22$), which was also significantly negative ($r = -0.701$, $p < 0.001$).

Discussion

Helicobacter pylori is the bacterial species responsible for the most common chronic gastrointestinal infection that causes gastroduodenal inflammation, ulceration, and increased mucosal permeability. These characteristics led us to hypothesize that *H. pylori* might interfere with the appearance of ASCA in the pathophysiology of SpA. We observed a negative correlation between the anti-*H. pylori* IgG and ASCA titers, and this negative correlation occurred for both ASCA subclasses (IgG and IgA). Furthermore, the same negative correlation was observed in CD. Remarkably, the frequency of anti-*H. pylori* positivity was significantly lower

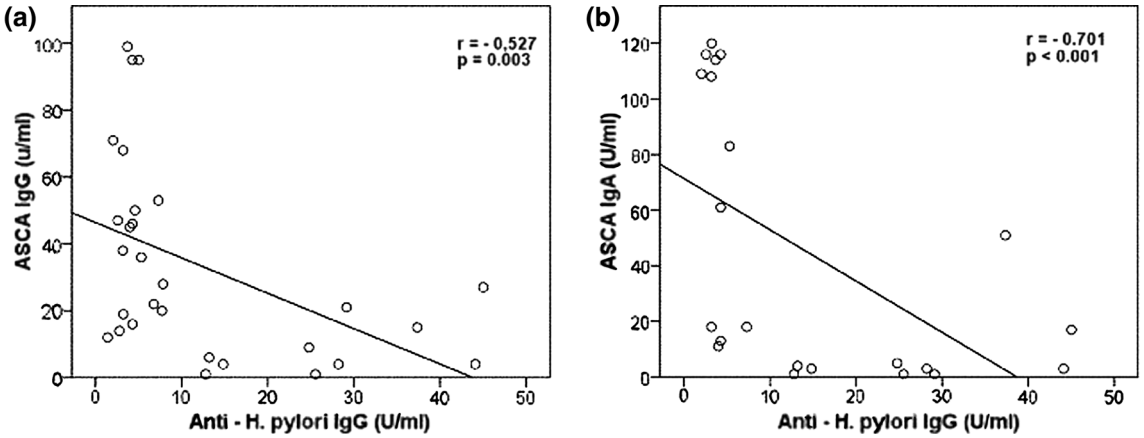

Fig. 2 **a** Correlation between ASCA IgG and anti-*H. pylori* IgG titers in Crohn disease patients in which at least one of these tests was positive ($n = 29$). **b** Correlation between ASCA IGA and anti-*H. pylori* IgG titers in Crohn disease patients in which at least one of these tests was positive ($n = 22$). *H. pylori*, *Helicobacter pylori*; ASCA, anti-*Saccharomyces cerevisiae* antibodies

in the CD group, which had a higher frequency of ASCA, than in the SpA group with the lower ASCA frequency.

These findings are consistent with previous results in the medical literature, which demonstrated that the frequency of anti-*H. pylori* antibodies is lower in patients with IBD than in healthy controls: 27.5 vs. 41.7 % [22], and 24 vs. 37 % [23]. These authors suggested a protective role for *H. pylori* infection against the appearance of IBD. This is consistent with the "hygiene hypothesis" whereby exposure to certain common bacterial species (*H. pylori* in this case) modulates immune activity and thereby reduces the incidence of intolerance to the commensal microbiome, which is supposed to be a key element of IBD pathogenesis [23]. In line with the "hygiene hypothesis", population studies have correlated lower rates of *H. pylori* infection and better hygienic conditions with higher rates of allergic diseases [27].

However, the role of *H. pylori* as an immunological modulator is controversial. It is possible that the *H. pylori* infection is just a bystander to some other infectious agent under poor hygienic conditions, as suggested by a Malaysian study that found no increase in the asthma prevalence in a population with poor hygienic conditions in combination with a low prevalence of *H. pylori* infection [28]. However, evidence from mechanistic studies demonstrated that dendritic cells exposed to *H. pylori* actually prevented the development of asthma in mice models by the induction of regulatory T cells, suggesting a direct role for *H. pylori* as a negative immunologic regulator [29, 30].

In our study, we observed that CD patients had a lower rate of *H. pylori* infection than SpA patients. Conversely, ASCA were more frequent in CD patients than in those with SpA. And in both groups, the ASCA titers were inversely correlated with the anti-*H. pylori* titers. These observations suggest a negative association between *H. pylori* infection and the presence of ASCA. However, our study has limitations that must be considered. First, its cross-sectional design does not allow inferences of causality. In addition, the number of cases in the study limits our results; the 12 % difference in the rates of ASCA positivity between the positive and negative anti-*H. pylori* IgG groups of axial SpA patients was not statistically significant with this sample size, and studies with larger populations will be required to assess this difference.

Also importantly, our study did not include normal subjects, because a very large sample size would be necessary to identify the few who were ASCA positive and allow a correlation analysis with the anti-*H. pylori* results. Thus, the question of a relationship between *H. pylori* and the presence of ASCA in healthy individuals without an inflammatory disease was not assessed. In addition, we cannot discuss whether *H. pylori* is a causative or protective agent for the onset of axial SpA. Our study only assessed the relationship between *H. pylori* infection and the presence of ASCA in patients who had already presented with axial SpA.

We must also note that in this study, we used serological tests as surrogate markers for *H. pylori* infection and intestinal inflammation. A number of diagnostic tests for *H. pylori* infection have been clinically established. Using ELISA for the detection of anti-*H. pylori* IgG in this study was due to its availability, low cost, ease of implementation, and status as a non-invasive method that poses no risks to the patient. In addition, serology is the only test that is unaffected by local changes in the stomach, which could lead to a low bacterial load and false-negative results for other tests such as the urea breath test [31]. Antibodies against *H. pylori* remain elevated despite the decrease in bacterial load that occurs after proton pump inhibitor therapy or gastrointestinal bleeding. Kuipers et al. [31]

demonstrated that *H. pylori* infection is acquired during youth, and the antibody concentrations do not change with age. The sensitivity of serology for the diagnosis of *H. pylori* infection is very high, with a reported value close to 100 % [20]. However, Feldman et al. [32] demonstrated that 60 % of patients who were cured of *H. pylori* infection had undetectable levels of anti-*H. pylori* antibodies after 18 months of treatment. The disappearance of anti-*H. pylori* antibodies after treatment is one criterion for the cure of *H. pylori* infection [20]. In our study, only five of the axial SpA subjects had a previous diagnosis of infection with *H. pylori* and received treatment with antibiotics and proton pump inhibitors prior to the survey. We kept these patients in the analysis, because the study aimed to investigate the relationship between the current presence of ASCA and anti-*H. pylori* IgG, not necessarily the current presence of active infection by *H. pylori*. Moreover, the presence of these treated cases did not affect our results.

Nevertheless, prospective and mechanistic studies using other methods to assess the gastrointestinal microbiome are needed to determine whether *H. pylori* alone is negatively correlated with ASCA, or if this correlation only exists between antibody titers. Another possible confounding factor for our conclusions would be the presence of other unmeasured microbial components of the microbiome associated with *H. pylori* infection that could be the actual modulators for the presence of ASCA rather than *H. pylori*. As the clinical and treatment features were quite similar between the positive and negative *H. pylori* groups, other common biases are unlikely to influence our results, particularly given the same bias would have to occur in both the SpA and CD groups, which seems improbable.

The importance of ASCA as markers of the disease pattern or severity in patients with SpA remains controversial. Andretta et al. [14] found no relationship between ASCA positivity and the clinical features of AS such as the presence of peripheral disease, uveitis, or disease activity as evaluated with the BASDAI. However, in SpA patients with ASCA present, Hoffmann et al. [33] observed higher levels of C-reactive protein and faster erythrocyte sedimentation rates, and Aydin et al. [15] observed increased radiological damage. In our study, we observed no significant differences in the clinical features of SpA or the disease impact between the positive and negative anti-*H. pylori* IgG groups, but our study lacked the statistical power to adequately address this question, and larger samples will be necessary.

In summary, this study showed that the presence of high titers of anti-*H. pylori* IgG is associated with low titers of ASCA in patients with axial SpA. We further demonstrated that this negative correlation also occurs in patients with CD. Moreover, we observed that anti-*H. pylori* IgG+ serology is less frequent in patients with CD than in patients with axial SpA. Studies with larger samples and different methods are necessary to investigate if *H. pylori* exposure exerts an effect against the development of autoimmune intestinal inflammation in SpA patients.

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Conflict of interest The authors have no conflict of interest.

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