

Effect of *Helicobacter pylori* and Eradication Therapy on Gastrointestinal Permeability. Implications for Patients with Seronegative Spondyloarthritis

VINCENZA Di LEO, RENATA D'INCA', MARIA B. BETTINI, MARTA PODSWIADEK, LEONARDO PUNZI, GAETANO MASTROPAOLO, and GIACOMO C. STURNIOLO

ABSTRACT. Objective. Disruption of intestinal barrier function, followed by increased antigen load, may possibly trigger joint inflammation. In seronegative spondyloarthritis (SpA) both gut inflammation and altered intestinal permeability have been reported. We evaluated the influence of *Helicobacter pylori* and nonsteroidal antiinflammatory drugs (NSAID) on gastrointestinal (GI) permeability in SpA. Twenty SpA patients (7 women, mean age 47 ± 13 SD yrs), 30 patients with endoscopic gastritis (EndG; 17 women, mean age 48 ± 14 yrs), and 35 healthy controls (16 women, mean age 40 ± 15 yrs) were studied. No patient was undergoing antisecretory therapy. In the SpA group, 8 patients were chronically taking NSAID and 12 took NSAID occasionally, none during the month before the study. All subjects were assessed for gastroduodenal (sucrose) and intestinal (lactulose/mannitol) permeability test and *H. pylori* status (urea breath test).

Results. *H. pylori* affected GI permeability in both SpA and EndG patients. After eradication therapy, sucrose excretion remained increased in SpA and reverted to normal in EndG patients, whereas lactulose/mannitol test became comparable to controls in both groups. SpA patients taking chronic NSAID had increased gastroduodenal permeability only when *H. pylori*-positive. In SpA patients, GI permeability did not correlate with clinical activity or biochemical inflammation.

Conclusion. In SpA, *H. pylori* and NSAID contribute to impaired GI permeability. Eradication therapy may help to maintain epithelial barrier function and possibly influence clinical improvement in patients with SpA. (J Rheumatol 2005;32:295–300)

Key Indexing Terms:

GASTROINTESTINAL PERMEABILITY
HELICOBACTER PYLORI

SERONEGATIVE SPONDYLOARTHRTIS
NONSTEROIDAL ANTIINFLAMMATORY DRUGS

The condition of intestinal mucosa has been linked to the development of inflammatory joint symptoms¹. Reactive arthritis (ReA) following enteric infection with Gram-negative bacteria and joint inflammation associated with inflammatory bowel diseases are well described²⁻⁴. Sulfasalazine, a drug used in spondyloarthritis (SpA), exerts its action on both intestinal and joint inflammation⁵ and may modify microbial flora by decreasing the numbers of enterobacteria⁶.

Enteric bacteria may trigger systemic inflammation by impairing intestinal epithelial permeability⁷. The hypothesis

is that, once tolerance toward intestinal bacteria and their products is lost, inflammation can be induced and maintained in the intestinal mucosa and in the joints⁸. Indeed, there are several reports of increased gastrointestinal (GI) permeability in rheumatic disease⁹⁻¹² and of inflammatory changes in the small bowel mucosa of rheumatic patients¹³, supporting the role of the gut during joint inflammation.

Effects of antimicrobial therapy on the course of rheumatic diseases are controversial and mechanisms of action are unclear¹⁴⁻¹⁶. A recent study reported the effectiveness of eradication therapy for *Helicobacter pylori* in reducing disease severity in rheumatoid arthritis, suggesting a possible pathogenic role for this bacterium¹⁷. Altered gastroduodenal permeability is associated with *H. pylori* infection and may be involved in the onset of local diseases and complications, and possibly foster systemic diseases^{18,19}.

Nonsteroidal antiinflammatory drugs (NSAID), which are widely used in rheumatology, represent an additional factor affecting GI barrier function²⁰. This may be involved in the pathogenesis of NSAID induced mucosal injury²¹, but may also reflect a secondary phenomenon²². Increased gastroduodenal permeability has been reported after short term NSAID use²³.

Seronegative SpA is characterized by absence of serum

From the Gastroenterology Section, Department of Surgical and Gastroenterological Sciences, and Division of Rheumatology, Department of Clinical and Surgical Sciences, University of Padova, Padova, Italy.

V. Di Leo, MD, PhD, Research Fellow; R. D'Inca', MD, Assistant Professor; M.B. Bettini, MD, Attending Physician; G. Mastropaolo, MD, Assistant Professor; G.C. Sturniolo, MD, Associate Professor, Chief, Gastroenterology Section Department of Surgical and Gastroenterological Sciences; M. Podswiadek, MD, PhD Student; L. Punzi, MD, Associate Professor, Division of Rheumatology, Department of Clinical and Surgical Sciences.

Address reprint requests to Prof. G.C. Sturniolo, Department of Surgical and Gastroenterological Sciences, Gastroenterology Section, Ospedale Civile, Via Giustiniani 2, 35128 Padova, Italy.

E-mail: gc.sturniolo@unipd.it

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rheumatoid factor and involvement of axial-peripheral joints. The main types of arthritis in this group are represented by ankylosing spondylitis (AS), ReA, psoriatic arthritis (PsA), and undifferentiated seronegative SpA. Studies in idiopathic or reactive spondylitis show similar patterns in both intestinal inflammation and permeability^{9,24,25}.

Considering the few available data, the aims of our study were to characterize GI permeability in patients with PsA and undifferentiated seronegative SpA and to relate it to *H. pylori* status and NSAID therapy.

MATERIALS AND METHODS

Patients. Twenty patients with SpA (7 women, mean age 47 ± 13 SD yrs, range 23–62) were enrolled in the study. According to the European Spondylarthropathy Study Group criteria²⁶, 13 had psoriatic arthritis and 7 undifferentiated seronegative spondyloarthritis. Thirty patients (17 women, mean age 48 ± 14 SD yrs, range 25–71) undergoing upper GI endoscopy for dyspeptic symptoms and having macroscopic gastritis (endoscopic gastritis: EndG) volunteered as positive controls. Thirty-five healthy volunteers (16 women, mean age 40 ± 15 SD yrs, range 23–47), with no upper GI symptoms and negative urea breath test, acted as negative controls. No control received any medication during the previous month.

No patient or control was taking proton pump inhibitors or any other kind of antisecretory therapy.

The study was approved by the local ethics committee and informed consent was obtained from all patients and controls.

Study protocol. GI permeability was assessed after overnight fasting. Each patient drank a solution containing 10 g lactulose, 5 g mannitol, and 40 g sucrose in 100 ml water. During the following 6 hours, urine was collected in a container with 2 ml chlorhexidine gluconate to prevent bacterial degradation. No food or liquid intake (except water) was allowed during urine collection. Urine samples were immediately refrigerated and taken to the laboratory within 24 hours. The volume of 6-hour urine pool was recorded and stored in aliquots at -20°C until assayed. All patients and controls were screened for *H. pylori* infection by urea breath test, which has over 95% accuracy²⁷. All *H. pylori*-positive patients were treated with triple eradication therapy (omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg, twice daily for 1 week, followed by omeprazole 20 mg/day for 1 month). GI permeability and urea breath tests for *H. pylori* were repeated after 3 months from the end of treatment.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also measured in SpA patients to assess inflammation. All patients were screened with antitransglutaminase antibodies to rule out celiac disease.

SpA patients ($n = 4$) complaining of upper GI symptoms and all the positive controls underwent gastroscopy to assess presence and grade of gastroduodenal pathology 1 week after gastroduodenal permeability was assessed.

Evaluation Of gastroduodenal permeability. Sucrose was used to measure gastroduodenal permeability. The sucrose assay is based on its hydrolyzation by β -fructosidase to glucose and fructose. Glucose is measured by the hexokinase method²⁸; the resulting reduced nicotinamide adenine dinucleotide phosphate (NADP) is measured at 340 nm. Results are expressed as percentage of excretion of the ingested dose of sucrose (%S). The presence of glucose, fructose, or lactose in physiological concentrations did not influence the accuracy of the assay.

Evaluation of intestinal permeability. Intestinal permeability was evaluated by the lactulose/mannitol ratio, to overcome the effect of extramucosal factors (i.e., gastric emptying, transit time, renal clearance).

Mannitol was assayed indirectly by measurement of formaldehyde produced during periodic acid oxidation²⁹: 0.5 cc of periodic acid (0.03 mol/l in 0.25 mol/l sulfuric acid) was added to the urine sample (0.2 ml). After 10

min at room temperature, 0.5 ml stannous chloride (0.125 mol/l) was added to the solution. Oxidation of the stannous chloride in stannic acid by the periodic acid turns the solution into a milky precipitate. The precipitate was dissolved in 5 ml of chromotropic acid reagent. After vigorous shaking, the tube was placed in a boiling water bath for 30 min. Once cooled, the solution was made up to 25 ml with distilled water and the temperature was stabilized at 25°C in a water bath. At this temperature, the color remains stable for several hours. The optical density was read at 560 nm. The reagent blank, made up containing 1 ml of distilled water and treated throughout in the same manner as the sample tubes, was measured at the same time.

The lactulose assay is based on its hydrolyzation by β -galactosidase in fructose and galactose²⁷ and enzymatic processing of fructose by hexokinase. The resulting reduced NADP is measured at 340 nm. The intra- and interassay variability was 4% and 5.5%, respectively. The presence of glucose, fructose, or lactose in physiological concentrations did not influence the accuracy of the assay. The urinary excretion of each molecule was expressed as a percentage of the dose administered and the permeability index (lactulose/mannitol) was calculated.

Statistic analysis. As the data distribution was non-Gaussian, data are expressed as median with 25th and 75th centiles, unless otherwise indicated. Comparisons among groups were made by nonparametric tests, in particular by Mann-Whitney test for unpaired data and Wilcoxon rank-sum test for paired data, as appropriate. Correlation between variables was estimated using Pearson's correlation coefficient. A p value < 0.05 was considered significant.

RESULTS

SpA patients had a mean duration of 79 ± 80 SD months (range 6–336) for joint symptoms and 123 ± 83 months (range 24–252) for psoriasis. The number of involved joints was established by physical examination, radiology, and bone scintigraphy. The average number of involved joints, according to the Ritchie index modified for SpA³⁰, was 8 ± 5 ; 8 patients had axial disease as well. At study entry, 8 patients were chronically taking NSAID (indomethacin 100 mg/day) and 12 were taking NSAID occasionally; none, however, during the month before the study. Two patients were taking low dose steroids (methylprednisolone 4 mg/day), one also taking longterm NSAID. All SpA patients were interviewed before the start of the study: 4 of them complained of upper GI symptoms, whereas none had stool abnormalities.

Median values for GI permeability in SpA and EndG patients and healthy controls are shown in Table 1. Overall, compared to healthy controls, sucrose excretion was significantly increased in both groups, whereas the lactulose/mannitol test values were higher only in SpA patients.

GI permeability and *H. pylori*. In the SpA group 35% (7/20) of patients had a positive urea breath test for *H. pylori*, compared to 80% (24/30) in the EndG group.

GI permeability was significantly affected by *H. pylori* infection.

In SpA patients who were positive for *H. pylori*, sucrose excretion was significantly increased compared to the healthy controls ($p < 0.001$) and the SpA patients who were negative for *H. pylori* ($p < 0.05$). Similarly, sucrose excretion was increased in patients with EndG who were positive for *H. pylori* compared to the healthy controls ($p < 0.001$)

Table 1. GI permeability mean values in patients with seronegative SpA and endoscopic gastritis (EndG).

	n	% S			L/M		
		Median	25th Centile	75th Centile	Median	25th Centile	75th Centile
SpA	20	0.165*	0.085	0.395	0.022*	0.009	0.032
EndG	30	0.185*	0.095	0.375	0.019	0.010	0.030
Healthy controls	35	0.080	0.053	0.098	0.013	0.010	0.016

* p < 0.005 vs healthy controls. % S: percentage of sucrose excretion. L/M: lactulose-mannitol test.

and the EndG patients who were negative for *H. pylori* (p < 0.01; Table 2).

In both SpA and EndG groups, lactulose/mannitol test values were not different from the healthy controls in *H. pylori*-negative patients (p > 0.05), whereas intestinal permeability was enhanced in *H. pylori*-positive subjects (p < 0.05; Table 2).

All patients with *H. pylori* infection were prescribed triple eradication therapy and were recommended to repeat the urea breath and gastroduodenal permeability tests after 3 months. All 7 SpA patients who were *H. pylori*-positive and 13 of 23 EndG patients who were *H. pylori*-positive repeated the tests. All patients had negative urea breath test, and

sucrose permeability was significantly improved. At the end of the treatment period, sucrose excretion was decreased in 4 and unchanged in 3 of the 7 SpA patients (Figure 1). The median value of sucrose excretion in the SpA treated patients was significantly lower compared to pretreatment values (p < 0.05), but still significantly increased compared to results in healthy controls (p < 0.05). Among the 13 EndG patients who underwent eradication therapy, sucrose permeability was improved in 8 patients and unchanged in 5 (Figure 1). The median value of sucrose excretion in these EndG patients was significantly decreased compared to pretreatment values (p < 0.05) and was not different from the healthy controls (p = nonsignificant; Table 2).

Table 2. GI permeability according to *H. pylori* status in patients with seronegative SpA and endoscopic gastritis (EndG) before and after eradication therapy with omeprazole 20 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid for 7 days, followed by 30 days omeprazole 20 mg/day. Data are expressed as median (25th/75th centiles) (number of patients).

	SpA		EndG	
	% S	L/M	% S	L/M
<i>H. pylori</i> -	0.110 (0.080/0.140) (13)	0.017 (0.009/0.028) (13)	0.063 (0.035/0.094) (6)	0.010 (0.006/0.021) (6)
<i>H. pylori</i> + pre-eradication	0.385 (0.203/0.718)*† (7)	0.030 (0.022/0.043)*† (7)	0.230 (0.172–0.490)*† (24)	0.021 (0.015/0.030)*† (24)
<i>H. pylori</i> + post-eradication	0.160 (0.085/0.185)*†† (7)	0.010 (0.009/0.016)†† (7)	0.145 (0.124/0.220)†† (13)	0.016 (0.015/0.019)†† (13)

* p < 0.05 vs healthy controls. † p < 0.05 for *H. pylori* - vs *H. pylori*+. †† p < 0.05 pre vs post-eradication therapy. % S: percentage of sucrose excretion. L/M: lactulose/mannitol test.

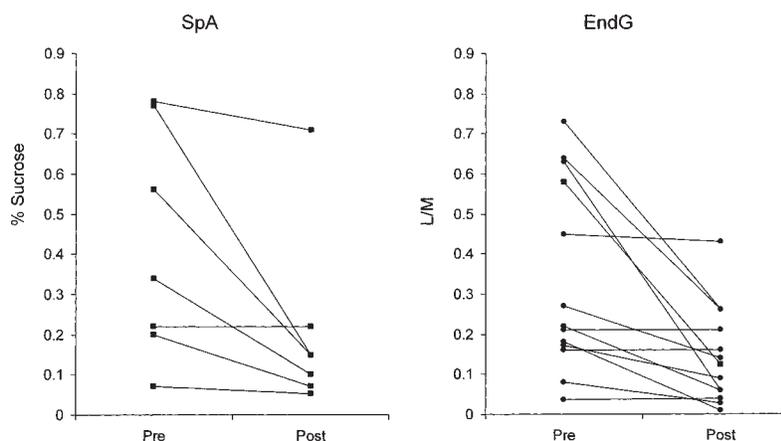


Figure 1. Sucrose excretion pre and post *H. pylori* eradication therapy in patients with seronegative SpA and with endoscopic gastritis (EndG).

In both SpA and EndG patients, after *H. pylori* eradication the median lactulose/mannitol test values were comparable to healthy control values (Table 2).

GI permeability and NSAID in SpA patients. In the SpA group, 8 patients had been regularly taking NSAID for at least 6 months. In these patients the median sucrose excretion was 0.180% of the oral dose (0.050–0.373), comparable to patients who were not taking continuous NSAID [0.130% of oral dose (0.085–0.310); $p = \text{NS}$]. After stratification for *H. pylori* status and NSAID therapy, sucrose excretion was found to be affected by *H. pylori* status rather than by NSAID therapy (Figure 2).

In the 8 SpA patients who were taking longterm NSAID, the mean lactulose/mannitol test value was significantly increased compared to patients who were not taking NSAID: 0.034 (0.023–0.041) and 0.010 (0.009–0.026), respectively ($p < 0.05$). The effect of NSAID on small bowel permeability was confirmed after stratification by *H. pylori* status (Figure 2).

GI permeability and clinical and biochemical indicators in SpA patients. We found no relation between sucrose excretion and lactulose/mannitol test results and disease type (PsA or undifferentiated seronegative SpA), duration of disease, axial or peripheral involvement, and number of distal peripheral joints involved.

Finally, biochemical inflammatory activity, measured by ESR and CRP levels, was found to be not related to GI permeability.

DISCUSSION

We observed that *H. pylori* increases gastrointestinal permeability; in patients with SpA permeability is only partially restored after eradication therapy.

Baseline gastric permeability is enhanced in patients with limited systemic sclerosis¹², whereas it is reported to be normal in patients with AS and their first-degree relatives²⁴. In

our series of SpA patients, none with AS, sucrose excretion was increased compared to healthy controls and was not different from patients with endoscopic gastritis. Sucrose permeability is a useful way of screening for gastric damage³¹, although its relationship with *H. pylori* is controversial^{18,19,32,33}. It has been reported that gastric barrier function is compromised by *H. pylori* induced neutrophil infiltration¹⁹. When our patients were stratified according to *H. pylori* status, gastroduodenal permeability was found to be affected by the actual infection rather than by mucosal integrity. Indeed, in EndG patients who were *H. pylori*-positive we found increased sucrose excretion whenever neutrophil inflammation was present, but the overall increased gastric permeability was not related to the degree of inflammation (data not shown).

Intestinal permeability was also affected by *H. pylori* status in both SpA and EndG patients. Although *H. pylori* has been shown to disrupt barrier function in intestinal cell lines^{34,35}, there is no evidence that it may exert such an effect in humans. It has been reported that cagA-positive *H. pylori* may colonize the duodenum³⁶, which may partially explain the increased intestinal permeability. However, in our *H. pylori* patients, GI permeability was increased irrespective of the bacterial virulence.

Improvement of gastric permeability after eradication therapy has been reported in mice infected by *Helicobacter felis*³⁷, whereas there are no reports for humans. In SpA patients sucrose excretion remained increased after *H. pylori* eradication, whereas in the EndG patients eradication was followed by normalization of sucrose permeability. In contrast, in both SpA and EndG patients, lactulose/mannitol test values were comparable to healthy controls after eradication therapy. These findings suggest that the gastroduodenal barrier or its repair mechanisms might be primarily impaired in a subgroup of patients with SpA. It is also possible that in SpA patients neutrophil infiltration persists

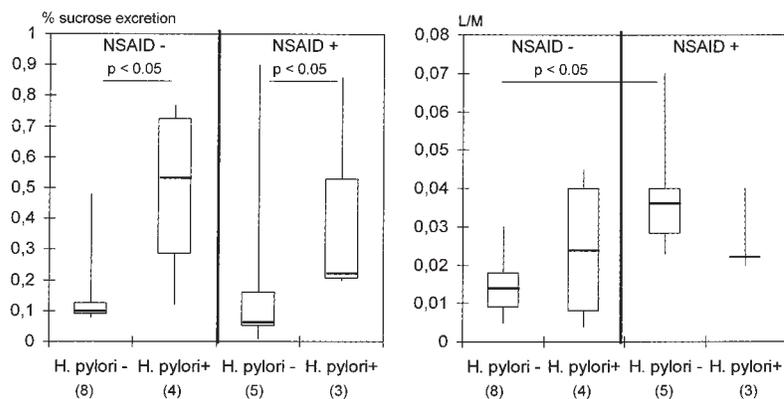


Figure 2. GI permeability in patients with seronegative SpA according to NSAID therapy and *H. pylori* status. Data of the box plots are given as median plus 25th/75th centiles. Bars represent the total range of values. Values in parentheses represent number of patients. L/M: lactulose/mannitol test.

longer after eradication of the bacterium, which usually abolishes active inflammation in 2 months³⁸.

NSAID directly affect epithelial barrier function of the whole GI tract²⁰. In our study, the prominent role of *H. pylori* in impairing gastric epithelial function was reiterated even when compared with NSAID. SpA patients taking indomethacin for at least 6 months had normal gastroduodenal permeability only if they were *H. pylori*-negative, similarly to patients who were not taking NSAID. Gastric mucosal adaptation occurring during chronic use of NSAID³⁹ may be impaired by *H. pylori*⁴⁰. This could contribute to understanding why eradication did not restore gastroduodenal permeability in patients with SpA.

In rheumatic diseases increased intestinal permeability has frequently been reported⁴¹, although it is difficult to distinguish a primary defect from the NSAID induced defect. It has been suggested that in SpA intestinal damage might antedate development of bowel or joint symptoms²⁴. We confirmed that intestinal permeability was increased by NSAID and, as a result, in our SpA patients the median value of the lactulose/mannitol test was significantly increased compared to healthy controls.

We found no relationship between GI permeability and severity of arthritis. Similar results have been reported in pediatric¹¹ and adult populations¹² of rheumatic patients. The intestinal barrier is a dynamic setting, whose status changes under physiologic and pathologic conditions⁴². It is possible that in patients with SpA increased intestinal permeability and active joint inflammation may occur separately. Nevertheless, this event may be associated with subclinical GI inflammation⁴³, and may have clinical implications in rheumatic patients⁴⁴ and also in their first-degree relatives⁴⁵.

Increased antigenic load could contribute to the perpetuation of GI inflammation, with possible systemic consequences. Moreover, impaired barrier function is involved in the onset of GI lesions and bleeding in NSAID users⁴⁶. Therefore, strategies to prevent such damage should be encouraged. As *H. pylori* appears to be a major factor in altering epithelial permeability, we suggest investigation for *H. pylori* in patients with SpA, particularly in those who require longterm NSAID therapy.

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