Sacroiliitis Is Common in Crohn's Disease Patients with Perianal or Upper Gastrointestinal Involvement

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Background/Aims: Sacroiliitis (SI) is one of the most frequent extraintestinal manifestations in inflammatory bowel disease (IBD) patients, but the exact prevalence has not been evaluated in Asia. There are few data on the association between SI and other clinical features of IBD. The prevalence of SI was evaluated using computed tomography (CT) and the phenotypic parameters associated with SI in Korean IBD patients were determined. **Methods:** Eighty-two patients with ulcerative colitis (UC) and 81 patients with Crohn's disease (CD) were evaluated clinically. The presence of SI was evaluated using bone window setting of abdomino-pelvic CT images by two radiologists. **Results:** The prevalence rates of SI were 12.2% and 21.0% in the UC and CD groups, respectively. There was no relationship between the localization or extent of intestinal inflammation and the presence of SI in the UC group. Multivariate analyses confirmed that perianal and upper-gastrointestinal (from the mouth through to the jejunum) diseases were associated with the occurrence of SI in the CD group ($p=0.026$ and $p=0.047$, respectively). **Conclusions:** SI was as common among Korean IBD patients as among Western patients. Perianal or upper-gastrointestinal involvement is associated with SI in CD patients. (*Gut Liver* 2010;4:338-344)

Key Words: Inflammatory bowel disease; Extraintestinal manifestation; Sacroiliitis; Prevalence

INTRODUCTION

Idiopathic inflammatory bowel disease (IBD) affects predominantly the gastrointestinal system but is associated with a large number of extraintestinal manifestations (EIMs). EIMs contribute significantly to the morbidity and mortality of IBD.¹ Studies have demonstrated that the EIMs of IBD were much less common among Asians than among Western populations.^{2,3} However, most of these studies used subjective diagnostic modalities based on physical examinations, symptom questionnaires, and simple radiological examinations. No study has determined the precise prevalence of EIMs using objective diagnostic modalities.

Rheumatic complications are particularly prevalent in EIMs of IBD. Among these, axial involvement may vary from subclinical sacroiliitis (SI) to clinical evidence of inflammatory lower back pain to classic ankylosing spondylitis.⁴ SI is often asymptomatic and thus easily overlooked as an EIM of IBD, but is nevertheless considered one of the most common EIMs. It has been suggested that some subclinical SI can progress to overt ankylosing spondylitis,⁵ and delayed diagnosis and inappropriate treatment can contribute significantly to morbidity.⁶ The prevalence of radiological SI varied between 2% in a population study and 10-32% in hospital-based studies.⁵⁻⁹ Despite the prevalence of SI in IBD, there are few reports on the clinical phenotypes associated with SI. The exact prevalence of SI in Asians has not been evaluated.

Computed tomography (CT) and magnetic resonance

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imaging (MRI) are superior to other diagnostic modalities for evaluating the sacroiliac joint.^{6,10,11} However, these methods involve increased radiation exposure and additional costs for the patient. Sometimes IBD patients undergo abdominal CT for the evaluation of the extent and severity of the disease and the presence of complications. After postprocessing these abdominal CT images to the bone window setting, we use them for detecting SI.

Our aim in this cross-sectional clinical and radiological study was to investigate the prevalence of SI in Korean patients with ulcerative colitis (UC) and Crohn's disease (CD) and to evaluate the phenotypic parameters associated with SI in these patients.

MATERIALS AND METHODS

1. Patients

We evaluated 163 consecutive Korean patients with established diagnoses of CD or UC between January 2001 and March 2008. Except for two patients diagnosed with ankylosing spondylitis, none showed symptoms such as low back pain, morning stiffness, and buttock pain.

All of the patients underwent colonoscopy, gastroscopy, and abdominal CT. All patients with CD underwent small bowel enteroclysis. The diagnoses of CD and UC were based on clinical, endoscopic, and histological evaluations. The demographic and clinical data, including age, gender, age at disease onset, history of surgery, and disease duration, were recorded on a standardized form.

The Montreal classification was applied to describe CD subgroups: L1, disease limited to the terminal ileum; L2, disease location at any position between the cecum and rectum; L3, involvement of the terminal ileum and the colon; and L4, any disease location proximal to the terminal ileum; B1, non-stricturing, non-penetrating; B2, stricturing; and B3, penetrating.¹² According to the age at onset of CD, patients were divided into two groups: <18 and >18 years, to discriminate pediatric from adult-onset CD.

Endoscopic findings and the extent of UC were classified using the Mayo score system (0, normal; 1, mild with erythema, decreased vascular pattern, and mild friability; 2, moderate with marked erythema, absent vascular pattern, friability, and erosions; and 3, severe with spontaneous bleeding, and ulceration).¹³

2. Radiological evaluation

The presence of SI was evaluated using the original abdomino-pelvic CT images that were processed using the bone window setting. The CT images were evaluated independently by two experienced bone radiologists who

were blinded to the patients' clinical complaints and diagnoses. The severity of SI was scored using the New York grading system (0, normal; 1, suspicious; 2, localized sclerosis, erosion, and joint widening; 3, diffuse sclerosis, erosion, and widening; and 4, ankylosis).¹⁴ Radiological SI was diagnosed by the presence of at least unilateral SI grade 1, and only when both radiological assessors agreed. When two radiological assessors did not agree with the radiological SI, the end result was defined by a consensus between the investigators.

3. Statistical analysis

Differences in the clinical features among the UC and CD groups were evaluated using either a chi-square test or Fisher's exact test for categorical data and a t-test for quantitative data. Multivariate analysis was performed using logistic regression with SI and non-SI as dependent variables. All statistical tests were two-sided, and statistical significance was assigned to p values less than 0.05.

4. Ethics

The study protocol was approved by the Human Medical Research Committee of Kyung Hee University, Korea.

RESULTS

1. Prevalence of SI in UC and CD patients

Of the 163 patients (103 men, 60 women) in the study, 82 had UC (mean age, 42.7±13.8 years) and 81 had CD (mean age, 28.8±8.8 years). The mean disease duration was 18.0 months in the UC group and 32.1 months in the CD group.

Abnormalities of the sacroiliac joint on CT suggested SI

Table 1. Patient Characteristics in Ulcerative Colitis and Crohn's Disease

Characteristic	UC group (n=82)	CD group (n=81)	Total (n=163)
Age, yr	42.7±13.8*	28.8±8.8	35.8±13.6
Male, n (%)	44 (53.7)*	59 (72.8)	103 (63.1)
Disease duration, mo	18.0	32.1	25.0
ANCA, n (%)	30/73 (41.1)*	5/64 (7.8)	35/137 (25.5)
OR, n (%)	5 (6.1)*	27 (33.3)	32 (19.6)
SI, n (%)	10 (12.2)	17 (21.0)	27 (16.6)

UC, ulcerative colitis; CD, Crohn's disease; ANCA, anti-neutrophil cytoplasmic antibody; OR, history of surgery; SI, sacroiliitis.

*p<0.05 vs. CD.

in 27/163 patients: 10 (12.2%) of the UC patients and 17 (21.0%) of the CD patients. The UC patients were older, had shorter disease duration, and had fewer previous operations compared with the CD patients (Table 1). Among the 27 patients identified with SI, seven had grade 1; 14, grade 2; four, grade 3; and two, grade 4 (Table 2). Only two patients met the criteria for ankylosing spondylitis.

2. Association of SI with clinical parameters in the UC group

Age, gender, disease duration, and surgical history were not associated with the presence of SI. The distribution of intestinal disease among the UC patients was as follows: 18.3% proctitis, 35.4% left-side colitis, and 46.3% pancolitis. In the SI group, disease locations were 10.0% proctitis, 20.0% left-side colitis, and 70.0% pancolitis. Compared with the non-SI group, there is no statistical significance in the proportion of the pancolitis (70.0% vs 43.1%, $p=0.019$). The disease activity on endoscopy was mild in 22.0%, moderate in 53.7%, and severe in 24.4%

Table 2. Radiographic Classification of Sacroiliitis in the Study Groups, according to the New York Criteria

Sacroiliitis	Total, n	CD, n	UC, n
F/M	11/16	5/12	6/4
Grade I	7	4	3
Grade II	14	11	3
Grade III	4	1	3
Grade IV	2	1	1

F/M, female/male; UC, ulcerative colitis; CD, Crohn's disease.

of the UC patients, and the SI prevalence rates according to disease activity were 0, 13.6, and 20.0%, respectively ($p=0.155$). Disease distribution and endoscopic severity were not associated with the presence of SI. Anti-neutrophil cytoplasmic antibody (ANCA) was present in 41.1% (30/73 patients) and was more prevalent in the SI group than in the non-SI group (70% vs 36.5%, respectively; $p=0.046$, Table 3).

3. Association of SI with clinical parameters in the CD group

Age, gender, disease duration, and surgical history were not associated with the presence of SI. After classifying the CD group using the Montreal classification, we investigated whether each clinical parameter was associated with the presence of SI (Table 4). According to the age at onset of CD, 15 (18.5%) patients were ≤ 18 years old and 66 (81.5%) were > 18 years (Table 4). The prevalence of SI in the ≤ 18 years group (6/15, 40.0%) was significantly higher than in the > 18 years group (11/66, 16.7%; $p=0.045$). The proportions of L1 to L4 patients were 17.3, 14.8, 67.9, and 18.5%, respectively. There was no difference in the proportion of L1, L2 and L3 in the SI and non-SI patients. The prevalence of upper disease (L4: from the mouth to the jejunum) in SI patients was significantly higher than in non-SI patients ($p=0.007$).

The proportions of patients classified as B1, B2, and B3 were 50.6, 25.9, and 23.5%, respectively. There was no difference in the proportion of B1, B2, and B3 in the SI and non-SI patients. Thirty-nine (48.1%) CD patients had perianal disease. The SI patients (76.5%) had a higher rate of perianal disease than the non-SI patients (40.6%)

Table 3. Prevalence of Clinical Parameters of Ulcerative Colitis according to the Presence of Sacroiliitis

Parameter	Total (n=82)	Non-SI (n=72)	SI (n=10)	p-value
Disease duration, mo	18.0	17.5	21.6	0.760
Male, n (%)	44 (53.7)	40 (55.6)	4 (40.0)	0.355
Location, n (%)				0.109
Proctitis	15 (18.3)	14 (19.4)	1 (10.0)	
Left side	29 (35.4)	27 (37.5)	2 (20.0)	
Pancolitis	38 (46.3)	31 (43.1)	7 (70.0)	
Endoscopic finding, n (%)				0.155
Mild	18 (22.0)	18 (25.0)	0 (0.0)	
Moderate	44 (53.7)	38 (52.8)	6 (60.0)	
Severe	20 (24.4)	16 (22.2)	4 (40.0)	
ANCA, n (%)	30/73 (41.1)	23/63 (36.5)	7/10 (70.0)	0.046
OR, n (%)	5 (6.0)	5 (6.9)	0	0.392
Period after diagnosis, n (%)				0.661
<1 yr group*	61 (74.4)	53 (73.6)	8 (80.0)	
>1 yr group	21 (25.6)	19 (26.4)	2 (20.0)	

SI, sacroiliitis; ANCA, anti-neutrophil cytoplasmic antibody; OR, history of surgery.

*Patients who were diagnosed within less than 1 year.

Table 4. Prevalence of Clinical Parameters of Crohn's Disease Using the Montreal Classification, according to the Presence of Sacroiliitis

Parameter	Total (n=81)	Non-SI (n=64)	SI (n=17)	p-value
Disease duration, mo	32.1	27.9	48.1	0.218
Male, n (%)	59 (72.8)	40 (73.4)	12 (70.6)	0.814
Age at diagnosis, n (%)				0.045
≤18 yr	15 (18.5)	9/15 (60.0)	6/15 (40.0)	
>18 yr	66 (81.5)	55/66 (83.3)	11/66 (16.7)	
Location, n (%)				0.498
L1	14 (17.3)	11 (17.2)	3 (17.6)	
L2	12 (14.8)	11 (17.2)	1 (5.9)	
L3	55 (67.9)	42 (65.6)	13 (76.5)	
L4	15 (18.5)	8 (12.5)	7 (41.2)	0.007
Behavior, n (%)				0.226
B1	41 (50.6)	32 (50.0)	9 (52.9)	
B2	21 (25.9)	19 (29.7)	2 (11.8)	
B3	19 (23.5)	13 (20.3)	6 (35.3)	
P	39 (48.1)	26 (40.6)	13 (76.5)	0.009
OR, n (%)	27 (33.3)	21 (32.8)	6 (35.3)	0.847
Period after diagnosis, n (%)				0.05
<1 yr group	50 (61.7)	43 (67.2)	7 (41.2)	
>1 yr group	31 (38.3)	21 (32.8)	10 (58.8)	

SI, sacroiliitis; L1, terminal ileum; L2, colon; L3, ileocolon; L4, from the mouth to the jejunum; B1, non-stricturing and non-penetrating; B2, stricturing; B3, penetrating; P, perianal disease; OR, history of surgery.

($p=0.009$). With respect to the occurrence of SI, significant associations were found with age at onset of CD, L4 or perianal disease, but not with disease behavior (B1-B3), or disease location (L1-L3).

In the UC and CD groups, we found no association between the occurrence of SI and disease duration (UC group: Spearman's correlation coefficient $\rho=0.395$, $p=0.259$; CD group: Spearman's correlation coefficient $\rho=0.277$, $p=0.281$).

Newly diagnosed patients, i.e., those who were diagnosed within less than 1 year, included 61 (74.4%) of the 82 patients with UC and 50 (61.7%) of the 81 patients with CD. In the UC group, the prevalence of SI was 13.1% (8/61) in the <1 year group and 9.5% (2/21) in the >1 year group; these values were not significantly different ($p=0.66$). In the CD group, the prevalence of SI was higher in the >1 year group (32.3%) than in the <1 year group (14%), but the difference was not statistically significant ($p=0.05$).

4. Multivariate analysis

Logistic regression was used to investigate whether ANCA, perianal involvement, or upper gastrointestinal involvement were independent risk factors for SI. Gender, age, disease duration, pancolitis, and a history of surgery were covariates. ANCA positivity in the UC group was not associated with the presence of SI (odds ratio [OR], 2.25; confidence interval [CI], 0.44-11.35; $p=0.323$). By

Table 5. Multivariate Analysis (Logistic Regression) with Sacroiliitis as the Dependent Variable

Multivariate		SI vs Non-SI		
		OR	95% CI	p-value
UC	Gender	0.45	0.10-2.12	0.324
	Age	0.96	0.90-1.03	0.271
	Disease duration	1.00	0.99-1.02	0.372
	>1 yr group	0.20	0.01-6.48	0.362
	ANCA	2.25	0.44-11.35	0.323
CD	Pancolitis	1.95	0.38-9.72	0.421
	Gender	0.68	0.17-2.76	0.594
	Age	0.96	0.88-1.05	0.461
	Age at onset of CD	0.32	0.65-1.52	0.150
	Disease duration	1.00	0.98-1.02	0.822
	>1 yr group	2.84	0.35-23.05	0.322
	Upper disease (L4)	5.50	1.2-24.5	0.026
	Perianal disease (p)	4.05	1.1-16.1	0.047

SI, sacroiliitis; OR, odds ratio; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease; ANCA, anti-neutrophil cytoplasmic antibody.

contrast, in the CD group, age at onset of CD was not associated with the presence of SI (OR, 0.31; CI, 0.06-1.52; $p=0.150$), but perianal (OR, 5.5; CI, 1.2-24.5; $p=0.026$) and upper gastrointestinal tract (L4; from the mouth through the jejunum) diseases (OR, 4.0; CI, 1.02-16.1; $p=0.047$) were significantly associated with a higher occurrence of SI (Table 5).

DISCUSSION

This study confirmed a high prevalence of SI in Korean IBD patients, and our results are consistent with those of Western studies.⁵⁻⁸ SI was identified in 12.2% of the patients with UC and 21.0% of the patients with CD. There is relatively little information on the prevalence of SI in Asians, and our study is believed to be the first to report on the prevalence of SI in Asians, as determined using bone window CT images.

A few Chinese studies have documented that EIMs of IBD are less common in Asian than Western countries.^{2,3} and the prevalence of EIMs of UC and CD was 5.7-14.0% and 19.0-22.3%, respectively. However, a study in Iran has reported that 31.4% of UC and 40.4% of CD patients may have one of the EIMs.¹⁵ An Indian study has reported that one or more of such EIMs occurred in 34.7% of UC patients.¹⁶ There has been considerable disagreement regarding the prevalence of joint involvement in Asian IBD patients. A study in China has documented that joint involvement was found in 2.3-7.1% in UC patients and 7.9-9.1% in CD patients.^{2,3} An Indian study has shown that peripheral arthritis occurred in 10.7% of UC patients,¹⁶ and another Korean study has shown that arthritic manifestations occurred in 19.6% of UC and 13.5% of CD patients.¹⁷ Thus, the prevalence of arthritic manifestations in IBD has been variously reported in Asia. There is controversy about the prevalence of EIMs and arthritic manifestations in Asian IBD patients as compared with Western IBD patients.

Asymptomatic SI has been described in 10-32% of patients and was the most frequent EIM of IBD from several Western studies.⁵⁻⁸ However, only a few reports are available regarding the prevalence of SI in Asian IBD patients: 14% in India, and 6.2% in Korea.^{16,17} Our results are consistent with those of Western studies and demonstrate that SI is as common in Korean patients with CD and UC as in Western patients. Further studies with more objective means of diagnosing EIMs are needed to discriminate the differences in the prevalences of EIMs between Eastern and Western countries.

The estimates of SI prevalence have varied widely, largely because of the differences in study composition and methodology. Many types of tests, including clinical examinations, plain film radiography, scintigraphy, CT, and MRI, have been used to evaluate the sacroiliac joint. Each modality has its limitations. Clinical examination requires patient cooperation, and plain film radiography detects abnormalities only in patients with advanced disease.^{11,18} Scintigraphy, although highly sensitive, lacks specificity as a diagnostic tool; it allows the detection of

early SI but fails to differentiate inflammatory from degenerative synovitis.¹⁹ Considering these limitations and the greater resolution of CT and MRI, several workers have advocated their routine use in the evaluation of the sacroiliac joint. Some studies have suggested that CT and MRI are more sensitive and specific than the combination of clinical examinations and plain film radiography.^{6,10,11} Nevertheless, CT involves increased radiation exposure, and MRI and CT are relatively expensive. As the patients with back symptoms were more likely to agree to CT or MRI, the inclusion of these patients might have introduced some selection bias. In our study, abdomino-pelvic CT was used to evaluate the extent and severity of the disease and the presence of complications. Therefore, our study was free from this selection bias. Moreover, no additional cost was involved, because these scans were easily converted to bone window CT images, which can detect SI more precisely. However, we recruited a population of patients with CD and UC from a tertiary referral center, which may reflect referral bias, although other studies have also involved tertiary centers.^{5,8} In addition, the inclusion of patients who had abdominal CT taken at the initial diagnosis, or at another point for a different reason, may reflect selection bias, as these patients might have had more severe and complicated disease.

In some studies, gastrointestinal inflammation was associated with spondyloarthropathy (SpA).²⁰⁻²³ The best evidence of this association was the presence of gut alterations, varying from an increased number of lymphoid follicles²⁰ to asymptomatic chronic intestinal inflammation,²¹⁻²³ in approximately 60% of the patients with SpA. We evaluated the prevalence of SI in patients with intestinal tuberculosis (TB), which has similar clinical, pathological, and endoscopic findings to CD (data were not shown). Among 39 TB patients, only one (2.6%) showed SI ($p=0.008$ vs CD). Our results indicated that intestinal inflammation is not the only cause of SI; other immunological mechanisms may also be involved in the development of SI.

In the present study, the phenotypic features of all of the patients with established CD were classified using the Montreal classification.²⁴ The association of SI with each phenotypic parameter as well as with gender, age, disease duration, and surgical history was investigated. There have been few data on the association of SI with clinical parameters in IBD patients. Only two Western studies have used plain film radiography to detect SI.^{8,25} Both of these have suggested that the extent of disease is not associated with occurrence of SI. One of them showed that perianal fistula is not associated with SI. However, our

results are different from these two studies. Gender, age, surgical history, disease location (L1-L3), and disease behavior (B1-B3) were not associated with SI, whereas perianal and upper gastrointestinal tract (L4; from the mouth to the jejunum) diseases were significantly associated with SI.

There is a controversy about whether SI is related to disease duration of IBD. In the present study, there was no association between SI and disease duration. This results is similar to study by McEniff *et al.*¹⁰ and Peeters *et al.*²⁵ But the disease duration of UC and CD patients were only 18.0 months and 32.1 months, respectively in our study. To determine whether SI is associated with disease duration, larger and longer follow-up studies are necessary.

Although we do not know the exact mechanism responsible for the increased prevalence of SI in the presence of perianal and upper gastrointestinal tract diseases, we postulate that patients with these conditions are more likely to have greater extraintestinal inflammation. The possibility that SI is another consequence of more severe immunological responses cannot be excluded. Beaugerie *et al.*²⁶ have reported that the presence of perianal disease at diagnosis was independently associated with increased risk for a subsequent 5-year disabling CD clinical course that required early aggressive therapy. In our study, the presence of perianal disease was an independent risk factor for the occurrence of SI (OR, 4.0; $p=0.047$). This supports the concept that perianal disease in CD represents increased immunological and inflammatory responses. Thus, CD patients with perianal disease should be examined more carefully for EIMs and SpA. Wagtmans *et al.*²⁷ have reported that patients with proximal CD tended to be younger at the time of diagnosis and more often presented with abdominal pain and malaise. In addition, patients with proximal CD did not undergo surgery as often as patients with lower tract disease alone, but the length of bowel that was resected tended to be greater in CD patients. In our study, patients with proximal CD had a significantly higher prevalence of SI (OR, 5.5; $p=0.026$). Consequently, proximal CD may be a clue to identifying the presence of EIMs or SpA. Further studies with larger populations are needed to evaluate the relationships among these phenotypic changes and other EIMs.

In case of asymptomatic SI patients with IBD, additional drugs besides conventional IBD medication do not need. But, it may be beneficial physical therapy and non-steroidal anti-inflammatory drugs in treating of symptomatic patient. IBD patients need to be carefully screened for inflammatory back pain as part of their routine fol-

low-up. Delayed diagnosis and inappropriate treatment such as immobilization can contribute significantly to morbidity in Ankylosing spondylitis; early initiation of spinal exercise programs can have important beneficial effect.

In conclusion, this analysis of Korean patients with IBD found a high prevalence of SI as an EIM of IBD, consistent with Western studies. In CD patients, perianal and upper gastrointestinal diseases are associated with a higher incidence of SI. Patients with these clinical findings should be evaluated for the presence of SI.

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