ORIGINAL ARTICLE

Inflammatory Articular Disease in Patients with Inflammatory Bowel Disease: Result of the Swiss IBD Cohort Study

Saskia Ditisheim, MD, Nicolas Fournier, PhD,† Pascal Juillerat, MD, MSc,‡ Valerie Pittet, PhD, MSc,† Pierre Michetti, MD,§ Cem Gabay, MD,‖ and Axel Finckh, MD‖ on behalf of the Swiss IBD Cohort Study Group*

Background: Inflammatory bowel diseases (IBD) are systemic conditions that commonly display extraintestinal manifestations. Inflammatory articular disease (IAD: axial or peripheral) is the most common extraintestinal manifestation. The aim of this study was to evaluate the prevalence and the clinical characteristics associated with IAD in patients with IBD.

Methods: We analyzed patients enrolled in the Swiss IBD cohort study. IAD was defined as persistent or recurrent joint pain with an inflammatory pattern (night pain, progressive relief during the day, morning stiffness lasting at least 30 minutes) or the presence of arthritis as diagnosed by the physicians. A multivariate logistic regression was performed to analyze which disease characteristics were independently associated with the presence of IAD.

Results: A total of 2353 patients with IBD, 1359 with Crohn's disease, and 994 with ulcerative colitis (UC) were included. Forty-four percent of patients fulfilled the criteria for IAD, whereas 14.5% presented with other extraintestinal manifestations. IAD was associated with Crohn's disease, with female sex, with older age, and generally in patients with more active intestinal disease. Only in UC, IAD was further associated with tobacco smoking and with increasing body mass index.

Conclusions: This population of patients with IBD displays a high prevalence of IAD. IAD was more strongly associated with Crohn's disease than UC. Other risk factors for IAD were female sex, advanced age, active digestive disease, and tobacco consumption in patients with UC, which is interesting given the established association between smoking and other inflammatory arthritides.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, inflammatory arthritides, spondyloarthropathy, Swiss IBD cohort study

Musculoskeletal disorders are well-recognized extraintestinal manifestations (EIM) of inflammatory bowel diseases (IBD). A similar etiopathogenesis has been postulated, based on genetic and immunological data.[1–4] The prevalence of inflammatory articular disease (IAD) in patients with IBD has been reported somewhere between 10% and 45%,[5–7] reflecting possible differences in study design and patient selection.[5,8–10] The pathogenic link between articular involvement and IBD is not yet fully understood. Some authors claim that the intestinal permeability may be higher both in patients suffering from IBD[11] and from spondyloarthropathies.[12] Several studies have demonstrated minimal or infraclinical digestive inflammation in patients with spondyloarthropathies or ankylosing spondylitis.[13–16] Crohn's disease (CD) and spondyloarthropathies may be a similar immune-mediated inflammatory disease with distinct phenotypes and different clinical, immunological, histopathological, and genetic findings.[3,16–18] Other common pathogenic pathways may involve the microbiome and distinct set of adhesion molecules.[19,20]

The aim of this study was to investigate the prevalence of IAD in a large multicentric cohort of well-characterized patients with IBD living in Switzerland, and to identify disease characteristics associated with the occurrence of IAD in patients with IBD.

MATERIALS AND METHODS

This is a cross-sectional study, nested within a prospective population-based cohort study of patients with IBD.

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From the *Clinique La Colline and Division of Gastroenterology and Hepatology, University Hospital of Geneva, Geneva, Switzerland; †Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland; ‡Division of Gastroenterology, Clinic for Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland; §Gastroenterology La Source-Beaulieu and Division of Gastroenterology and Hepatology, CHUV, Lausanne, Switzerland; and ‖Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland.

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Reprints: Axel Finckh, MD, Division of Rheumatology, University Hospital of Geneva, Avenue de Beau-Sejour 26, 1206 Geneva, Switzerland (e-mail: Axel.Finckh@hcuge.ch).

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Patients' Population

The Swiss IBD Cohort Study was initiated by the IBDnet, an interest group of the Swiss Society of Gastroenterology in collaboration with the five Swiss University centers and funded by the Swiss National Science Foundation since 2006 (www.ibdnet.ch). All local ethics committees approved the study. The study is described in detail elsewhere.[21] Briefly, patients were enrolled by gastroenterologists in university hospitals, regional hospitals, and private practices. Diagnosis of IBD was based on Lennard-Jones criteria[22] and was supported by endoscopic, radiological, or histological/surgical findings.[21] To be included, a diagnosis of IBD had to be established at least 4 months before the inclusion or the patients must have had at least one recurrence of symptoms. It is estimated that about 25% of all Swiss patients with IBD were enrolled up to 2013.[23] The cohort appears to be representative of the Swiss IBD population as the same likelihood to be enrolled in the cohort was observed between regions.[23]

Patients included in the present analysis were adults enrolled between July 2006 and December 2012. We excluded patients who did not complete the questionnaire.

Two distinct questionnaires were used to collect information at the time of patients' inclusion: one was completed by the physician—including disease characteristics and EIM—and one was completed by the patients. The patient self-reported questionnaire contained a set of questions on arthritides (see Questionnaire, Supplemental Digital Content 1, http://links.lww.com/IBD/B21). To validate our articular patient questionnaire, we administered the instrument to a control population of patients coming for a screening colonoscopy. In this group of 61 patients (mean age: 51.5 yrs, 59% male, 41% female), 67% reported some arthralgias, but only 13% fulfilled the criteria for IAD. These results suggest that the patient questionnaire is able to discriminate common arthralgias from IAD. As expected, the prevalence of self-reported arthralgias was fairly high in this elderly population. The "false-positive rate" of around 10% may be in part explained by some inflammatory presentations of osteoarthritis and by difficulties of some patients to qualify precisely their pain.

Outcome Variable

The outcome of interest for this analysis was the presence or absence of IAD in patients with IBD. IAD associated with IBD have been described and categorized using various criteria by different medical specialists.[5,24,25] Based on the clinical presentation, Orchard et al[5] have proposed a classification for peripheral IAD manifestations in 1998, distinguishing a pauciarticular flare-linked manifestation (type 1) and a polyarticular chronic manifestation (type 2). More recently, a consensus definition has proposed to regroup the articular manifestations of a group of interrelated conditions comprising ankylosing spondylitis, psoriasis, IBD, and reactive arthritis into axial and peripheral articular disease.[26,27]

In this study, we defined patients with IAD according to either (1) having had a documented episode of arthritis, confirmed by the gastroenterologist who included the patient or (2) fulfilling inflammatory pattern of pain on the patient questionnaire. An inflammatory pattern of joint pain was assessed as persistent or recurrent joint pain, associated with night pain, relief on movement, and morning stiffness lasting at least 30 minutes, based on published criteria.[26–29] To assess the robustness of our IAD definition, we performed a sensitivity analysis with a strict IAD definition relying exclusively on the physician-reported IAD. We categorized IAD in 2 subgroups: (1) pure peripheral articular disease and (2) IAD with axial involvement, with or without peripheral arthritis.

Exposure Variable and Predictors

We extracted from the Swiss IBD Cohort Study database demographic variables (age, sex), disease characteristics (symptom duration, EIM, type of IBD, disease activity and extension, familial history of IBD), treatment characteristics, lifestyle factors (tobacco smoke, body mass index), and generic quality of life measures (SF-36).

We used the Montreal classification for localization of intestinal disease at inclusion. In CD, L1 describes ileal disease, L2 colonic involvement, L3 ileocolonic disease, and L4 isolated upper gastrointestinal tract disease.[30] For UC, we categorized the condition into proctitis, left-sided colitis, and pancolitis. Severity and activity of digestive disease was assessed by the gastroenterologist according to the Crohn's Disease Activity Index for patients with CD[31] and the Modified Truelove and Witts Activity Index[32] for patients with UC. In CD, the cutoff for active disease was set at Crohn's Disease Activity Index $\geq$150,[33] and for UC, the cutoff for active disease was set at Modified Truelove and Witts Activity Index $\geq$10.[34] We used the WHO categorization for the body mass index (BMI).

Statistical Analysis

The statistical analysis was performed using Stata v. 13.1 for Windows (StataCorp., College Station, TX). First, continuous data distribution normality was assessed using normal Q–Q plots. Normally distributed variables were presented as mean $\pm$ SD, whereas nonnormally distributed variables were presented as median and interquartile range. Differences in mean values between two groups were assessed by the Student's t test for normally distributed variables. For nonnormally distributed variables, the Wilcoxon–Mann–Whitney rank-sum test was used to assess differences in distribution between two groups. Categorical variables were presented as raw counts and relative percentages. Differences in repartition of categorical variables among groups were assessed using the chi-squared test, or the Fisher's exact test in case of insufficient sample size. All statistical tests were two sided, and the significance level was set at 0.05. Confounding was a concern in this study because it is known from the literature that IAD is more often associated with CD, with other EIM of IBD and longer disease durations.[8,9,35,36] Because such differences may produce spurious associations, we used multivariate adjustments to overcome such confounding effects. We first examined univariate associations between disease characteristics and presence of IAD using logistic regression. We then performed a multivariable logistic regression to analyze which of the characteristics were independently associated with the presence of IAD.

RESULTS

A total of 2401 patients were included in the study. Patients with indeterminate colitis (n = 48) were excluded, leaving 2353 patients for the analysis (1359 patients with CD and 994 with patients with UC). Forty-four percent of all patients fulfilled our criteria for IAD, of which 42% presented a pure peripheral arthritis. Only 29% of patients with IAD reported ever consulting a rheumatologist for their symptoms (29% versus 7%, $P < 0.001$). In two-thirds of cases, IAD was corroborated both by patients and gastroenterologists. As expected, patients with IAD were more often on nonsteroidal anti-inflammatory drugs than patients without IAD (8% versus 3%, $P < 0.001$) and reported lower quality of life ($P < 0.001$) (Table 1).

In univariate analyses, IAD was more frequent in patients with CD than in patients with UC (64% versus 36%, $P < 0.001$). Furthermore, IAD was more common in women than in men (50% versus 37%, $P < 0.001$), in older than in younger patients (mean age, 43 versus 38 yr, $P < 0.001$), and in smokers than in

TABLE 1. Baseline Characteristics of IBD Patients with and Without IAD

Patients' Characteristics	Patients with IAD (N = 1036, 44%)	Patients Without IAD (N = 1317, 56%)	*P*
Median age (IQR), yrs	43 (32.5–54)	38 (28–50)	<0.001
Gender: female (%)	56.2	43.8	<0.001
Median BMI (IQR), kg/m^2	23.5 (21.1–26.5)	23.0 (22.9–25.9)	0.006
Diagnosis			
CD (%)	64.5	52.5	
UC (%)	35.5	47.5	<0.001
CD location			
L1 (ileal) (%)	31.5	29.3	
L2 (colonic) (%)	32.1	31.1	
L3 (ileocolonic) (%)	35.5	38.6	
L4 (upper gastrointestinal only) (%)	0.9	1.0	0.324
UC location			
Proctitis (%)	15.1	16.3	
Left-sided colitis (%)	46.1	39.7	
Pancolitis (%)	38.8	44.0	0.148
Intestinal disease activity			
CDAI >150 (%)	18.2	9.9	<0.001
MTWSI ≥10 (%)	7.7	6.4	0.496
Median intestinal symptoms duration (IQR; range), yrs	9 (4–18; 0–49)	7 (2–14; 0–49)	<0.001
Median articular symptoms duration (IQR; range)	6 (2–13; 0–61)	4 (1–8.5; 0–57)	<0.001
Tobacco			
Never smoked (%)	54.1	60.4	
Past or current smoker (%)	45.9	39.6	0.002
EIM (%)[a]	20.8	9.6	<0.001
Uveitis/iritis (%)	8.1	2.9	<0.001
Erythema nodosum (%)	6.7	2.3	<0.001
Pyoderma gangrenosum (%)	1.7	1.2	0.290
Aphthous ulcers/stomatitis (%)	9.3	2.7	<0.001
Primary sclerosing cholangitis (%)	0.9	2.1	0.015
Quality of life SF-36 score			
Physical (median, IQR)	46.2, 37.9–52.8	52.8, 45.3–56.6	<0.001
Mental (median, IQR)	45.0, 33.8–52.2	49.1, 40.7–54.3	<0.001
Seen by a rheumatologist (%)	29.2	7.4	<0.001
Positive IBD history in family (%)	14.9	11.4	0.015

[a]EIM excluding IAD.
CDAI, Crohn's Disease Activity Index; MTWSI, Modified Truelove and Witts Activity Index.

nonsmokers (46% versus 36%, $P < 0.001$). Patients with IAD had longer duration of intestinal symptoms than patients without articular symptoms (9 versus 7 yr, $P < 0.001$), whereas no difference was observed regarding the localization of intestinal disease, neither in UC nor in CD. A slightly higher BMI was seen in patients with IAD compared with patients without IAD (23.5 versus 23; $P = 0.006$). Patients with CD with active intestinal disease (Crohn's Disease Activity Index >150) had more often IAD (18% versus 10%, $P < 0.001$), whereas there was no difference regarding disease activity for patients with UC (Table 1). Patients with a positive family history of IBD were more frequently affected by IAD (15% versus 11%, $P = 0.02$). Patients with IAD also presented more commonly other EIM (21% versus 10%, $P < 0.001$). The most frequent EIM in patients with IAD was oral aphthosis (9.3%), followed by uveitis (8.1%) and erythema nodosum (6.7%). However, patients with another EIM typically presented more IAD than patients with only an intestinal disease (63% versus 41%).

Among the patients with IAD, peripheral arthritis was more frequently associated with active disease in CD (23.3% versus 14.5%, $P = 0.007$). Patients with peripheral IAD were also more likely to have other EIM (24.2% versus 18.2%, $P = 0.019$), in particular erythema nodosum ($P = 0.026$). No other patient characteristic was associated with a specific type of IAD (peripheral versus mixed; Table 2). Interestingly, 40.5% of all patients with

TABLE 2. Baseline Characteristics of IBD Patients with Pure Peripheral Versus Mixed IAD

Patients' Characteristics	Mixed, N = 598 (57.7%)	Pure Peripheral, N = 438 (42.3%)	*P*
Median age (median, IQR), yrs	43 (33–54)	42 (32–53)	0.239
Gender, female (%)	56.7	55.5	0.698
Median BMI (IQR), kg/m^2	23.7 (21.1–26.7)	23.4 (21.0–26.5)	0.450
Diagnosis			
CD (%)	63.6	65.8	
UC (%)	36.4	34.2	0.463
CD location			
L1 (ileal) (%)	34.1	28.0	
L2 (colonic) (%)	27.6	38.0	
L3 (ileocolonic) (%)	37.2	33.3	
L4 (upper gastrointestinal only) (%)	1.1	0.7	0.064
UC location			
Proctitis (%)	16.1	13.6	
Left-sided colitis (%)	47.4	44.2	
Pancolitis (%)	36.5	42.2	0.529
Intestinal disease activity			
CDAI >150 (%)	14.5	23.3	0.007
MTWAI ≥10 (%)	37.1	8.5	0.635
Intestinal symptoms duration (median, IQR, range), yrs	9, 4–18, 0–49	9, 4–18, 0–46	0.879
Articular symptoms duration (median, IQR, range), yrs	7, 2–13, 0–60	6, 2–13, 0–61	0.076
Tobacco			
Never smoked (%)	53.0	55.6	
Past or current smoker (%)	47.0	44.4	0.403
EIM (%)[a]	18.2	24.2	0.019
Uveitis/iritis (%)	7.0	9.6	0.137
Erythema nodosum (%)	5.2	8.7	0.026
Pyoderma gangrenosum (%)	1.3	2.3	0.252
Aphthous ulcers/stomatitis (%)	8.5	10.3	0.343
Primary sclerosing cholangitis (%)	1.0	0.7	0.548
Quality of life SF-36 score			
Physical (median, IQR)	45.5, 37.2–52.1	47.9, 40.1–53.8	0.002
Mental (median, IQR)	44.3, 33.7–51.7	45.8, 34.8–52.6	0.163
Seen by a rheumatologist (%)	30.1	27.5	0.410

[a]EIM excluding IAD.
CDAI, Crohn's Disease Activity Index; MTWSI, Modified Truelove and Witts Activity Index.

IAD experienced articular symptoms before onset of IBD symptoms. This occurred more frequently in patients with IAD with mixed involvement than with pure peripheral IAD involvement (45.6% versus 30.7%, $P < 0.001$). Approximately half of the patients with IAD link their articular symptoms to their IBD activity, in both subgroups (CD: 55.3% and UC: 46.7%).

Adjusting for all factors, the likelihood of presenting IAD was significantly higher in patients with CD compared with patients with UC (odds ratio [OR]: 1.52, 95% confidence interval [CI]: 1.21–1.84; $P < 0.001$) (Table 3). Furthermore, females appear to have approximately twice the risk of presenting an IAD as males (CD—OR: 1.83, 95% CI: 1.41–2.38, $P < 0.001$; UC—OR: 1.76, 95% CI: 1.29–2.41, $P < 0.001$). The risk of presenting IAD was increasing with age (trend test, $P < 0.001$). Tobacco consumption was not significantly associated with IAD in patients with CD, whereas patients with UC who smoke had more frequently IAD (OR: 1.57, 95% CI: 1.01–2.24, $P = 0.013$). Increased BMI was also associated with IAD in patients with UC (OR: 1.54 per increment of 10 kg/m^2, 95% CI: 1.05–2.26, $P = 0.03$) but not in patients with CD. Patients with active intestinal disease at the time of enrollment also tended to have more frequently IAD (CD—OR: 2.5, 95% CI: 1.64–3.74; UC—OR: 1.54, 95% CI, 0.87–2.72). There was no independent risk for IAD associated with the duration of IBD or with the localization of the intestinal involvement, neither in CD nor in UC. Sensitivity analysis with an alternative IAD definition restricted to physician-reported arthritis revealed similar results (data not shown).

DISCUSSION

In this large cohort of patients with IBD, IAD was present in 44% of patients, underscoring that articular involvement is frequent in this population. IAD may sometimes be neglected by specialists, as only one quarter (29%) of these patients reported ever seeing a rheumatologist. Axial involvement was the most common IAD presentation. IAD was more frequent in patients with CD than with UC, in females and in elderly. In patients with UC, IAD was further associated with smoking and overweight.

The prevalence of articular involvement reported in our cohort is higher than described in some other studies[5,6,8–10,37] but is consistent with what Turkcapar et al[7] described (46%). One possible explanation for the high prevalence of IAD in this study

TABLE 3. Multivariate Logistic Regression of Clinical Parameters Associated with the Presence of IAD

	Patients with CD			Patients with UC		
Outcome: IAD versus No IAD	OR	95% CI	*P*	OR	95% CI	*P*
Age, yrs						
<30	1 (ref)	—	—	1 (ref)	—	—
30–40	1.689	1.143–2.496	0.008	1.247	0.772–2.013	0.366
40–50	1.868	1.215–2.873	0.004	1.594	0.968–2.626	0.067
>50	2.321	1.479–3.645	<0.001	1.665	0.991–2.799	0.054
Gender						
Male	1 (ref)	—	—	1 (ref)	—	—
Female	1.832	1.385–2.424	<0.001	1.733	1.257–2.389	0.001
Smoking status at diagnosis						
Never smoked	1 (ref)	—	—	1 (ref)	—	—
Smoker	0.953	0.723–1.256	0.730	1.567	1.097–2.239	0.013
Disease duration since diagnosis (per 10 yrs)	0.923	0.783–1.089	0.343	1.204	0.996–1.456	0.055
BMI [per increment of 10 kg/m^2]	1.004	0.722–1.395	0.980	1.538	1.049–2.255	0.027
Disease location (CD)						
L1	1 (ref)	—	—			
L2	0.972	0.686–1.378	0.875			
L3	0.895	0.641–1.249	0.516			
Disease location (UC)						
Pancolitis				1 (ref)	—	—
Left-sided colitis				1.064	0.757–1.496	0.721
Proctitis				0.816	0.512–1.298	0.390
Disease activity at enrollment						
Inactive	1 (ref)	—	—	1 (ref)	—	—
Active[a]	2.476	1.639–3.741	<0.001	1.538	0.869–2.723	0.139

[a]Crohn's Disease Activity Index ≥150 for CD and Modified Truelove and Witts Activity Index ≥10 for UC.

might be relatively long disease duration in this cohort (median duration of IBD: 8 yr, interquartile range: 3–16 yr). Veloso et al[9] found that the prevalence of IAD doubles after 20 years of IBD, whereas Palm et al[8,10] described a 3-fold increase after 6 years of disease. Another explanation for the high prevalence of IAD is the preponderance of CD in the Swiss IBD cohort, whereas most other cohorts included more patients with UC, typically less associated with IAD.[5,8,10] We considered IAD that occurred at any time point during the course of the disease, as opposed to IAD present only at inclusion,[38] which could have further increased the prevalence of articular manifestations. Finally, it is possible that our definition of IAD overestimates the prevalence of IAD, as it also includes patient-defined articular symptoms, which may overdiagnose IAD by up to 10%, based on our validation study.

In accordance with the literature,[9,10,35] IAD occurs more frequently in patients with CD than in patients with UC in our cohort. We also found that IAD was significantly more common in patients with other EIM, such as cutaneous, ocular, or oral complications.[9,36] These findings corroborate the hypothesis of similar pathways of the different EIM.[20,39] Some authors have also described an association between IAD and the localization or the activity of the digestive disease.[9,10,36] We did not find any association between the occurrence of IAD and the localization of the intestinal involvement. Nevertheless, we could corroborate a trend to more IADs in patients with more active digestive disease, in particular in patients with CD with pure peripheral arthritis, as classically described.[5] However, associations with disease activity or specific therapies in a cross-sectional study design have to be interpreted with caution, as the use of immunomodulatory therapies may tend to weaken this association (bias towards the null). In UC, tobacco consumption was a risk factor for IAD, which is interesting given the established association between smoking and other inflammatory arthritides such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus.[40–42] Similarly, higher BMI was associated with UC, which is also an established risk factor for developing other articular diseases, such as psoriatic arthritis or rheumatoid arthritis. Intriguingly, the association with tobacco was not found in patients with CD, reproducing the differential effect of smoking on the intestinal disease in UC and CD.[43,44] Several mechanisms have been proposed to explain the effect of tobacco, such as modulation of cellular and humoral immunity, effect on gut permeability, colonic mucus, and mucosal blood flow. However, the precise cellular and molecular mechanisms are still unknown.[45–47]

One important finding of our study is that only 29% of patients having IAD ever consulted a rheumatologist for their articular symptoms. Potentially, many of the IAD symptoms are mild and self-limited and thus do not warrant specialized care. However, one cannot exclude some trivialization of the articular complaints by the treating physician confronted with patients with chronic digestive symptoms. Patients with IBD and concomitant IAD may warrant more aggressive therapy, suggesting that physicians following patients with IBD should search for articular manifestations, in particular if other EIM are present.

Strengths of this study are a large multicentric IBD cohort, confirmed by endoscopic and histological findings. Patients were recruited from a wide variety of settings, such as private practices, regional hospitals, and large tertiary centers. We do not believe that selection bias played a major role in the prevalence of IAD, as articular involvement was similar between the different recruitment sources ($P = 0.78$). The sensitivity analysis restricted to physician-reported arthritis showed similar results, suggesting that our results are not biased by patient-reported articular involvement. Some methodological issues of our study should be discussed. Our IAD definition included past articular involvement and may be affected by recall bias. However, potential recall bias is unlikely to be differential between the two groups, as all patients have IBD. Furthermore, we validated our patient questionnaire in a control population and demonstrated a good discrimination between inflammatory articular patterns and noninflammatory arthralgias. Our IAD definition further relies on the diagnosis of arthritis by nonspecialists, which is likely to result in underdiagnosis. In fact, in 35% of our IAD cases, the physician was not aware of the articular involvement. Furthermore, only one-third of these patients ever reported seeing a rheumatologist for a formal diagnosis. However, we believe that by combining patient and physician-reported articular involvement, we obtained a more reliable estimate of IAD prevalence. Another common limitation of cohort studies is missing data. In this cohort, the response rate to the patient questionnaire was of 72%. We do not believe that missingness in this study was differential between patients with or without IAD and is thus unlikely to bias our results in a significant way. We could not assess the temporality of IAD involvement in relation to the course of the digestive disease, thus our results represent a cumulated prevalence of IAD. Finally, anti-tumor necrosis factor and immunomodulatory medications may have influenced the presence of current IAD, as 20% of patients in this analysis were on anti-tumor necrosis factor at inclusion. However, our IAD definition included past arthritis episodes, before immunomodulatory therapies; thus, current medication is unlikely to have biased our overall IAD prevalence.

In conclusion, this study suggests that physicians need to be aware of the various presentations of articular involvement (axial, peripheral, mixed) to make an adequate diagnosis. Gastroenterologists need to identify patients with IBD with concomitant IAD, as these patients may probably need more aggressive management and are more likely to suffer from other extraintestinal complications.

REFERENCES

1. Rodriguez-Reyna TS, Martinez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World J Gastroenterol.* 2009;15:5517–5524.
2. Reveille JD. Genetics of spondyloarthritis—beyond the MHC. *Nat Rev Rheumatol.* 2012;8:296–304.
3. Laukens D, Georges M, Libioulle C, et al. Evidence for significant overlap between common risk variants for Crohn's disease and ankylosing spondylitis. *PLoS One.* 2010;5:e13795.

4. Brakenhoff LK, van der Heijde DM, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. *Gut*. 2011;60: 1426–1435.
5. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut*. 1998;42:387–391.
6. Salvarani C, Vlachonikolis IG, van der Heijde DM, et al. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol.* 2001;36:1307–1313.
7. Turkcapar N, Toruner M, Soykan I, et al. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. *Rheumatol Int.* 2006;26:663–668.
8. Palm O, Moum B, Ongre A, et al. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). *J Rheumatol.* 2002;29:511–515.
9. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol.* 1996;23:29–34.
10. Palm O, Moum B, Jahnsen J, et al. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). *Rheumatology (Oxford)*. 2001;40:1256–1261.
11. Peeters M, Ghoos Y, Maes B, et al. Increased permeability of macroscopically normal small bowel in Crohn's disease. *Dig Dis Sci.* 1994; 39:2170–2176.
12. Mielants H, Veys EM, De Vos M, et al. Increased intestinal permeability in ankylosing spondylitis. *Gut.* 1992;33:1150.
13. Mielants H, Veys EM, Cuvelier C, et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. *J Rheumatol.* 1995;22:2279–2284.
14. Leirisalo-Repo M, Turunen U, Stenman S, et al. High frequency of silent inflammatory bowel disease in spondyloarthropathy. *Arthritis Rheum.* 1994;37:23–31.
15. De Keyser F, Baeten D, Van den Bosch F, et al. Gut inflammation and spondyloarthropathies. *Curr Rheumatol Rep.* 2002;4:525–532.
16. Mielants H, De Keyser F, Baeten D, et al. Gut inflammation in the spondyloarthropathies. *Curr Rheumatol Rep.* 2005;7:188–194.
17. Orlando A, Renna S, Perricone G, et al. Gastrointestinal lesions associated with spondyloarthropathies. *World J Gastroenterol.* 2009;15:2443–2448.
18. Ramos PS, Criswell LA, Moser KL, et al. A comprehensive analysis of shared loci between systemic lupus erythematosus (SLE) and sixteen autoimmune diseases reveals limited genetic overlap. *PLoS Genet.* 2011;7:e1002406.
19. Rosenbaum JT, Lin P, Asquith M, et al. Does the microbiome play a causal role in spondyloarthritis? *Clin Rheumatol.* 2014;33:763–767.
20. Salmi M, Jalkanen S. Human leukocyte subpopulations from inflamed gut bind to joint vasculature using distinct sets of adhesion molecules. *J Immunol.* 2001;166:4650–4657.
21. Pittet V, Juillerat P, Mottet C, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *Int J Epidemiol.* 2009;38:922–931.
22. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl.* 1989;170:2–6; discussion 16–19.
23. Juillerat P, Pittet V, Bulliard JL, et al. Prevalence of inflammatory bowel disease in the Canton of Vaud (Switzerland): a population-based cohort study. *J Crohns Colitis.* 2008;2:131–141.
24. Cheung PP, Paternotte S, Burki V, et al. Performance of the Assessment in Spondyloarthritis International Society classification for axial and peripheral spondyloarthritis in an established clinical cohort: comparison with criteria sets of Amor and the European Spondyloarthropathy Study Group. *J Rheumatol.* 2012;39:816–821.
25. Scarpa R, Biondi Oriente C, Oriente P. The classification of psoriatic arthritis: what will happen in the future? *J Am Acad Dermatol.* 1997;36: 78–83.
26. Rudwaleit M, van der Heijde D, Landewe R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70:25–31.
27. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis.* 2009;68:777–783.
28. Rostom S, Dougados M, Gossec L. New tools for diagnosing spondyloarthropathy. *Joint Bone Spine.* 2010;77:108–114.
29. van den Berg R, de Hooge M, Rudwaleit M, et al. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis.* 2013;72:1646–1653.
30. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol.* 2005;19(suppl A):5–36.
31. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70:439–444.
32. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med.* 1994;330: 1841–1845.
33. Stange EF, Travis SP, Vermeire S, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut*. 2006;55(suppl 1):i1–15.
34. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007;132:763–786.
35. Gravallese EM, Kantrowitz FG. Arthritic manifestations of inflammatory bowel disease. *Am J Gastroenterol.* 1988;83:703–709.
36. Rankin GB, Watts HD, Melnyk CS, et al. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology*. 1979;77:914–920.
37. Gran JT, Husby G. Joint manifestations in gastrointestinal diseases. 1. Pathophysiological aspects, ulcerative colitis and Crohn's disease. *Dig Dis.* 1992;10:274–294.
38. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol.* 2011;106:110–119.
39. Grant AJ, Lalor PF, Salmi M, et al. Homing of mucosal lymphocytes to the liver in the pathogenesis of hepatic complications of inflammatory bowel disease. *Lancet*. 2002;359:150–157.
40. Harel-Meir M, Sherer Y, Shoenfeld Y. Tobacco smoking and autoimmune rheumatic diseases. *Nat Clin Pract Rheumatol.* 2007;3:707–715.
41. Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum.* 2001;31:146–159.
42. Ciurea A, Finckh A. Smoking and spondyloarthritis. *Joint Bone Spine.* 2013;80:234–235.
43. Somerville KW, Logan RF, Edmond M, et al. Smoking and Crohn's disease. *Br Med J (Clin Res Ed).* 1984;289:954–956.
44. Cosnes J. Smoking, physical activity, nutrition and lifestyle: environmental factors and their impact on IBD. *Dig Dis.* 2010;28:411–417.
45. Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis.* 2004;10:848–859.
46. Rom O, Avezov K, Aizenbud D, et al. Cigarette smoking and inflammation revisited. *Respir Physiol Neurobiol.* 2013;187:5–10.
47. Parkes GC, Whelan K, Lindsay JO. Smoking in inflammatory bowel disease: impact on disease course and insights into the aetiology of its effect. *J Crohns Colitis.* 2014;8:717–725.