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Classifying Back Pain and Peripheral Joint Complaints in Inflammatory Bowel Disease Patients: A Prospective Longitudinal Follow-up Study

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Abstract

Background and Aims: Peripheral joint complaints [pJTC] and chronic back pain [CBP] are the most common extra-intestinal manifestations in patients with inflammatory bowel disease [IBD]. This prospective study evaluates variables associated with joint/back pain, including IBD disease activity.
Methods: IBD patients with back pain ≥ 3 months and/or peripheral joint pain/swelling [*n* = 155], and IBD patients without joint complaints [*n* = 100; controls], were followed for a period of 1 year. Patients were classified as having SpondyloArthritis [SpA] according to several sets of criteria. Statistical analysis included logistic regression models and linear mixed model analysis.
Results: Of the 155 patients with joint/back pain, 13 had chronic back pain, 80 peripheral joint complaints, and 62 axial and peripheral joint complaints. Smoking, female gender, and IBD disease activity were independently associated with IBD joint/back pain. The Assessment in Spondyloarthritis International Society criteria for axial and peripheral SpA were fulfilled in 12.3% of patients, with 9.7% [*n* = 15] receiving a rheumatological diagnosis of arthritis. During the 12-month follow-up, the majority of the patients reporting joint/back pain remained stable.
Conclusions: In our cohort, the majority of IBD patients reported joint/back pain and SpA was relatively common. To facilitate effective care, gastroenterologists should be aware of the various features of SpA to classify joint complaints and, by making use of an efficient referral algorithm, to refer CBP patients to the rheumatologist.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; arthropathy; spondyloarthritis

1. Introduction

Arthropathies are the most common extra-intestinal manifestations of inflammatory bowel disease [IBD], affecting approximately 30% of the patients.[1,2] Symptoms may be debilitating and have a considerable impact on quality of life.[3,4] IBD-associated arthropathies can be divided into inflammatory and non-inflammatory joint pain and may involve both axial and peripheral joints. Non-inflammatory joint pain, or arthralgia, is one of the most common complaints in daily IBD practice, but has not yet been studied systematically.[3] Joint and back pain [hereafter referred to as 'joint/back pain'] are the most important clinical manifestations of IBD-associated arthropathies.

For the gastroenterologist, joint/back pain can be challenging symptoms to diagnose and many have difficulties in differentiating arthralgia from arthritis. Since gastroenterologists are, in general, unfamiliar with the diagnosis and management of joint/back pain, it seems warranted that IBD joint complaints should be classified according to existing rheumatological standards, thus allowing appropriate multidisciplinary management. Moreover, gastroenterologists mostly apply the Oxford criteria[5] to classify peripheral joint complaints, based on two different types according to articular involvement. Type 1 [oligoarticular] peripheral arthritis includes patients with less than five joints involved, evidence of joint swelling, and acute but self-limiting attacks. Type 2 [polyarticular] peripheral arthritis includes patients with five or more symmetrical affected joints, joint swelling, and a chronic character. Although the Oxford criteria distinguish these two types of peripheral joint complaints, this classification has limited utility for the physician in daily clinical practice. More importantly, these criteria are only applicable to arthritis and not to arthralgia. Rheumatologists therefore generally ignore the Oxford criteria and classify arthritis associated with IBD within the group of SpondyloArthritis [SpA] disorders.[6] SpA is a group of rheumatic diseases characterised by inflammation of the spine and the sacroiliac [SI] joints. This often results in pain and/or stiffness of the spine and neck. Inflammation may affect other regions besides, including the peripheral joints, tendons, eyes, skin, and/or gut.

In order to develop a multidisciplinary care pathway for IBD patients with joint complaints, we rigorously characterised peripheral joint complaints [pJTC] and chronic back pain [CBP] according to SpA criteria sets. In addition, we sought to determine which variables were associated with the onset of IBD joint complaints and which predicted long-term outcome. With this aim in mind, we carried out a prospective, longitudinal follow-up study of IBD patients with back pain and/or peripheral joint complaints.

2. Methods

2.1. Study population

From July 2009 to February 2010, all IBD patients visiting the IBD outpatient clinic of the department of Gastroenterology and Hepatology of the Leiden University Medical Center [LUMC], The Netherlands, were asked to complete a questionnaire to assess the presence of joint complaints. The questions concerned experience of: [1] CBP, defined as back pain for ≥ 3 months; [2] CBP for ≥ 3 months during the past year; [3] current pJTC [pain and/or joint swelling]; and [4] pJTC during the past year. Patients with self-reported joint/back pain were then invited to attend the JOINT outpatient clinic, a multidisciplinary clinic dedicated to IBD patients with joint complaints. This clinic was jointly established by the Department of Gastroenterology and Hepatology and the Department of Rheumatology, with the aim of expanding knowledge of IBD joint complaints, especially in the area of diagnosis and medical management. Patients with evident joint swelling and/or radiologically proven sacroiliitis were directly referred for rheumatological care. All IBD patients without joint/back pain during the previous year served as controls, and were also invited to attend the multi disciplinary clinic. To avoid high inclusion rates influencing the quality of patient care, and since only one clinical researcher was able to perform physical and rheumatological examinations, inclusion was limited to 255 patients. The study was approved by the institutional medical ethical committee of the LUMC, and patients signed a written informed consent before study enrolment.

2.2. Study design and data collection

All IBD patients with and without self-reported joint/back pain, who signed informed consent, were seen at the JOINT outpatient clinic at study inclusion and at 1 year follow-up. During the 12-month study period, patients were asked to complete monthly questionnaires assessing IBD disease activity and spine and/or peripheral joint scores. When no response was received within 1 week, a reminder email or letter was sent out, followed by a telephone call.

During the baseline visit, a routine medical history was taken and data on extra-intestinal manifestations were collected from all participants, including common IBD-related eye and skin manifestations such as acute anterior uveitis and erythema nodosum. The musculoskeletal history included back pain, enthesitis, arthritis, and dactylitis. The family history included IBD, SpA (including ankylosing spondylitis [AS]), acute anterior uveitis, psoriasis, and reactive arthritis. In addition to the routine physical examination, a rheumatological examination was performed in all IBD patients by a well-trained clinical researcher, including a detailed assessment of the number of tender and swollen joints. Furthermore, the presence of dactylitis was registered and enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score [MASES] index.[7] Assessment of spinal mobility was performed using the modified Schober test, lateral spinal flexion, cervical rotation, occiput-to-wall distance [OWD], chest expansion, and the intermalleolar distance.[8] The Bath Ankylosing Spondylitis Metrology Index [BASMI] was calculated, ranging from 0–10.[9] In the BASMI, the tragus-to-wall distance is used and derived from the OWD by adding 8 cm. The value zero in the OWD is equivalent to a score of zero in the BASMI calculation. The higher the BASMI score, the more severe the patient's limitation of axial movement. Spinal disease activity and function were assessed using the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI][10] and the Bath Ankylosing Spondylitis Functional Index [BASFI].[11] Laboratory assessments included erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]. Human leukocyte antigen-B27 [HLA-B27] was only typed in patients with CBP and/or peripheral joint complaints. Radiographs of the pelvis [anterior-posterior view], the lumbar and cervical spine [lateral view], and the most painful peripheral joints were performed in patients with joint/back pain.

Following the baseline assessment, patients were categorised into two study groups:

1. Patients with joint/back pain: CBP for ≥ 3 months and/or pJTC currently or during the previous year.
2. Patients without joint/back pain: no back pain or pJTC during the previous year.

2.3. Definitions

a. Crohn's disease [CD] disease activity was assessed according to the Harvey-Bradshaw Index [HBI][12]; ulcerative colitis [UC] disease activity was assessed using the Simple Clinical Colitis Activity Index [SCCAI].[13] A score > 4 reflects active disease.

b. Arthralgia was defined as joint pain without swelling; arthritis as joint pain with swelling.
c. Overall and nocturnal pain of the spine and peripheral joint pain during the previous week were separately scored on an 11-point numeric rating scale [NRS] ranging from 0 [no pain] to 10 [worst possible pain].[14]
d. Disease activity of the spine and disease activity of the peripheral joints during the previous week were scored, separately, on an 11-point NRS where 0 is inactive disease and 10 is extremely active disease.
e. Patients were classified as SpA according to the Amor[15] European Spondyloarthropathy Study Group [ESSG][16] Assessment of SpondyloArthritis international Society [ASAS][17,18] and modified New York [mNY] criteria.[19]

2.4. SpA classifications

In short, the Amor criteria for SpA consist of a scoring system of eight clinical features [1–2 points per feature], radiographic sacroiliitis [3 points], HLA-B27 [2 points], and a good response to non-steroidal anti-inflammatory drugs [NSAIDs] [2 points]. IBD is one of the clinical features receiving 2 points. A score of 6 or more classifies a patient as having SpA. In the ESSG criteria, patients with IBD and inflammatory back pain [according to the ESSG standard] and/or arthritis [past or present asymmetrical arthritis or arthritis predominantly in the lower limbs] are classified as SpA. ASAS developed two SpA criteria sets to classify patients with predominantly axial SpA [axSpA] and with predominantly peripheral SpA [pSpA]. Patients with IBD and CBP for ≥ 3 months and age at onset of back pain < 45 years can be classified as axSpA if sacroiliitis on radiograph or magnetic resonance imaging [MRI] is present and/or if HLA-B27 with at least one other SpA feature is present. An IBD patient with arthritis [usually predominantly lower limbs and/or asymmetrical arthritis], enthesitis, or dactylitis should be classified as pSpA. According to the mNY criteria, patients with AS based on radiographic sacroiliitis and the clinical criteria CBP for ≥ 3 months are classified as SpA [see Supplementary data available at *ECCO-JCC* online].

2.5. Statistics

Continuous variables were described with mean ± SD and categorical variables as proportions with percentages. T-tests were used for comparing continuous variables among the two study groups and Fisher's exact and chi-square tests were used for comparing categorical variables. Logistic regression models, with joint/back pain as the dependent variable, were used to assess variables associated with joint/back pain in IBD. First, univariate analyses were performed for several variables, including age, gender, type of IBD, IBD-associated surgery, active IBD [HBI or SCCAI > 4],

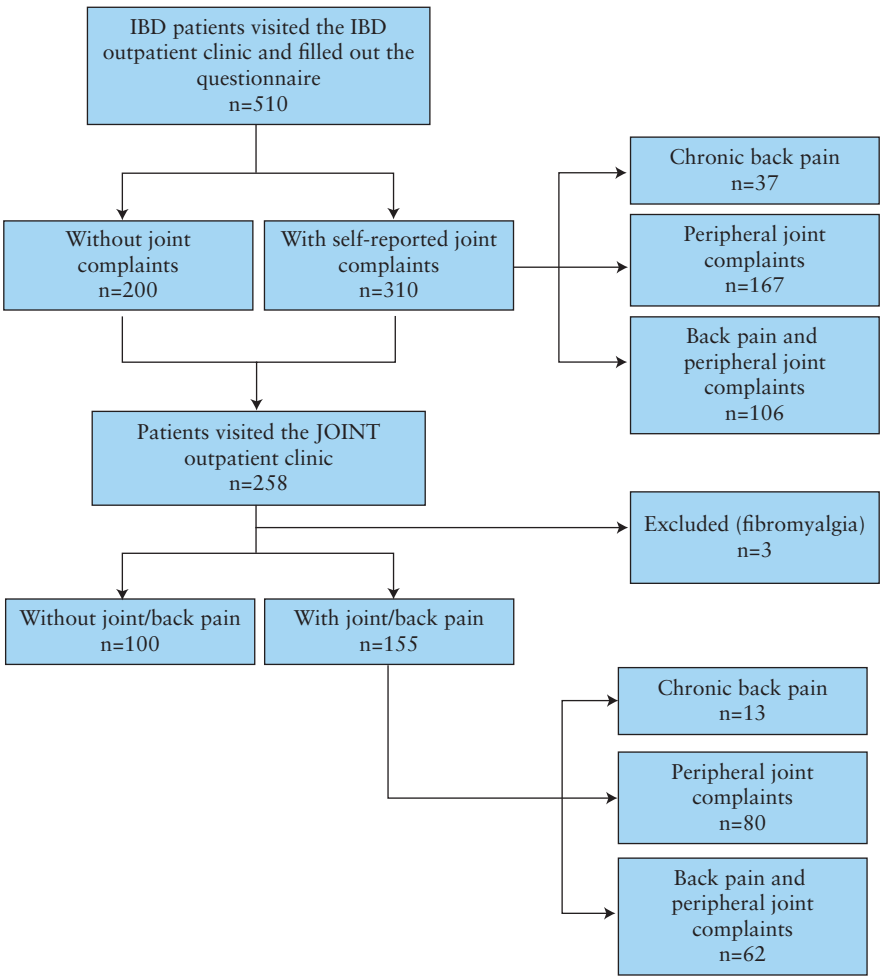

Figure 1. Patient inclusion flow chart.

smoking, family history for SpA, and cutaneous, ocular, and joint manifestations. Second, variables with a statistical level of $p < 0.1$ in the univariate analyses were included in the multivariate analyses. Linear mixed model analyses were performed to investigate whether IBD disease activity is associated with a worsening [eg an increased score] in the following items throughout follow-up: 1] disease activity of the spine; 2] general and nocturnal pain of the spine; 3] disease activity of the peripheral joints; 4] general and nocturnal pain of the peripheral joints. Patients were included as random variables, time points and IBD disease activity as fixed variables, and the outcome measures fixed as dependent variables. All analyses were performed using SPSS version 20; p-values < 0.05 were considered significant.

3. Results

3.1. Patients

In total, 510 IBD patients completed the questionnaire on joint complaints at the IBD outpatient clinic of the LUMC: 321 patients with Crohn's disease [CD], 186 with ulcerative colitis [UC], and 3 with indeterminate colitis [IC]. Of these, 310 [60.8%] patients reported joint complaints: 12% back pain only, 54% pJTC only, and 34% both [Figure 1]. The percentage of patients complaining about joint pain was higher in CD [65%] compared with UC [49%]. Subsequently, since only one clinical researcher was well trained in the assessment and examination of joint complaints, inclusion was limited to 255 patients [50%]. These 255 IBD patients signed

Table 1. Clinical and demographic characteristics of the study population at baseline [Visit 1].

	IBD with joint/back pain [n = 155]	IBD without joint/back pain [n = 100]	p-Value
Type of IBD, *n*			
Crohn's disease	121 [78.1%]	65 [65.0%]	0.03
Ulcerative colitis	34 [21.9%]	35 [35.0%]	
Male, *n*	46 [29.7%]	51 [51.0%]	0.001
Age at inclusion [years], mean ± SD	43.4 ± 13.6	42.7 ± 13.5	0.71
Age of IBD onset [years], mean ± SD	27.5 ± 11.3	26.0 ± 10.0	0.28
IBD disease duration [years], mean ± SD	15.4 ± 11.8	16.2 ± 11.0	0.56
Arthropathy onset in relation to IBD diagnosis			
•CBP	84% after/16% before	-	
•pJTC	80% after/20% before	-	
Arthropathy onset after IBD diagnosis [years]			
•CBP in CD[n = 46]/UC[n = 17]	14.7 ± 12.6/17.8 ± 10.5 [ns]	-	
•pJTC in CD[n = 86]/UC[n = 26]	11.6 ± 10.5/13.0 ± 9.6 [ns]	-	
Smoker, *n*	47 [30.0%]	13 [13.0%]	0.001
Montreal classification:			0.06
Location CD, *n*	n = 121	n = 65	
L1 ileal	34 [28.1%]	12 [18.5%]	
L2 colonic	27 [22.3%]	13 [20.0%]	
L3 ileocolonic	52 [43.0%]	31 [47.7%]	
L4 upper	-	2 [3.1%]	
L1-3+L4	8 [6.6%]	7 [10.8%]	
Behaviour CD, *n*			0.07
B1 non-stricturing/penetrating	77 [63.6%]	32 [49.2%]	
B2 stricturing	24 [19.8%]	14 [21.5%]	
B3 penetrating	20 [16.5%]	19 [29.2%]	
+ Perianal disease	37 [30.6%]	18 [27.7%]	
Extension UC, *n*	n = 34	n =35	0.23
E1 ulcerative proctitis	5 [14.7%]	2 [5.7%]	
E2 left-sided UC	13 [38.2%]	10 [28.6%]	
E3 extensive UC [pancolitis]	16 [47.1%]	23 [65.7%]	
IBD-related surgery, *n*	68 [43.9%]	39 [39.0%]	0.44
Family history SpA,[a] *n*	45 [29.0%]	29 [29.0%]	1.0
Extra-intestinal manifestations,[b] *n*			
Skin	27 [17.4%]	7 [7.0%]	0.04
Eye	22 [14.2%]	5 [5.0%]	0.02
Current medication use, *n*			
5-ASA [mesa, sulfa]	24 [15.5%]	27 [27.0%]	0.03
Steroids	11 [7.1%]	3 [3.0%]	0.16
Immunosuppressive drugs [Aza/6MP/MTX]	34 [21.9%]	21 [21.0%]	0.86
Anti-TNF	42 [27.1%]	30 [30.0%]	0.61
None	44 [28.4%]	19 [19.0%]	0.09

SD, standard deviation; IBD, inflammatory bowel disease; CBP, central back pain; pJTC, peripheral joint complaints; CD, Crohn's disease; UC, ulcerative colitis; SpA, spondyloarthritis; 5-ASA [mesa, sulfa], 5-aminosalicylates [mesalazine, sulfasalizine]; AZA, azathiopurine; 6MP, 6-mercaptopurine; MTX, methotrexate; TNF, tumour necrosis factor; ns, not significant.

[a]Family history SpA: ankylosing spondylitis, reactive arthritis, psoriasis, IBD, uveitis, all according to the definition of the ASAS criteria.

[b]Skin: psoriasis, erythema nodosum, pyoderma gangrenosum. Eye: acute anterior uveitis.

informed consent and attended the multidisciplinary clinic, of whom 155 [60.1%] were assigned to the study group with joint/back pain, whereas 100 [38.8%] patients without joint/back pain served as controls. The clinical and demographic characteristics of all patients are presented in Table 1. For 80–84% of patients, the onset of CBP and pJTC followed the IBD diagnosis and was on average more than a decade after diagnosis, with a trend towards pJTC starting a few years earlier than CBP [Table 1]. Only 16–20% developed joint/back pain prior to the diagnosis of IBD. Patients with IBD and joint/back pain were more often diagnosed with CD [p = 0.03], were more frequently female [p = 0.001], were more often smokers [p = 0.001], were more likely to have cutaneous manifestations [psoriasis, erythema nodosum, pyoderma gangrenosum] [p = 0.04], and acute anterior uveitis [p = 0.02] compared with patients with IBD without joint/back pain. The Montreal classification did not reveal subtypes more prone to developing joint/back pain. In addition, previous IBD-related surgery or a family history of SpA was not associated with the development of joint/back pain.

Of the 155 patients with joint/back pain, 80 patients [51.6%] reported pJTC only, 13 patients [8.4%] reported CBP only, and 62 patients [40.0%] reported axial as well as peripheral joint involvement [Table 2]. Over 50% of pJTC patients reported the hand [32.5%] and the knee [17.5%] as the most frequently affected joints, whereas 80.0% of patients reported involvement of more than one joint. At physical examination, 98 [63.2%] patients had ≥ 1 tender joint, and 48 [31.0%] patients had ≥ 1 tender pressure point for enthesitis. Only 52 IBD patients with evident joint swelling and signs of inflammation seen during rheumatological examination or on the radiographs were referred to the rheumatologist. Based on physical examination performed by the rheumatologist, 15 patients [9.7%] were diagnosed with arthritis and all could be classified as showing type 1 peripheral joint complaints according to the Oxford criteria. In addition, one [0.7%] patient was diagnosed with dactylitis, one [0.7%] patient with enthesitis, and two [1.4%] patients with tendinitis. Following radiographic assessment of all 75 CBP patients, 5 patients [6.7%] showed sacroiliitis and 1 patient was diagnosed with

Table 2. Characteristics of 155 inflammatory bowel disease [IBD] patients with self-reported joint and/or back pain.

	Chronic back pain [n = 13]	Peripheral joint complaints [n = 80]	Both [n = 62]	p-Value
Type of IBD, n				0.6
Crohn's disease	10 [76.9%]	65 [81.3%]	46 [74.2%]	
Ulcerative colitis	3 [23.1%]	15 [18.8%]	16 [25.8%]	
Male, n	6 [46.2%]	21 [26.3%]	19 [30.6%]	0.34
Age at inclusion [years], mean ± SD	38.2 ± 13.8	41.9 ± 13.5	46.2 ± 13.2	0.06
Age of IBD onset [years], mean ± SD	27.0 ± 14.0	33.0 ± 11.6	48.0 ± 13.5	0.25
IBD disease duration [years], mean ± SD	21.0 ± 19.8	33.0 ± 77.2	6.0 ± 6.7	0.21
Location [most painful] peripheral joints, n				0.16
Shoulder	-	10 [12.5%]	6 [9.7%]	
Elbow	-	10 [12.5%]	2 [3.2%]	
Wrist	-	9 [11.3%]	7 [11.3%]	
Hand	-	26 [32.5%]	22 [35.5%]	
Hip	-	1 [1.3%]	4 [6.5%]	
Knee	-	14 [17.5%]	17 [27.4%]	
Ankle	-	6 [7.5%]	1 [1.6%]	
Feet	-	4 [5.0%]	3 [4.8%]	
Distribution, n				0.22
Monoarticular	-	16 [20.0%]	6 [9.8%]	
Oligoarticular	-	32 [40.0%]	30 [48.3%]	
Polyarticular	-	32 [40.0%]	26 [41.9%]	
SpA features, n				
Arthritis [a]	0 [0.0%]	8 [10.0%]	7 [11.3%]	0.45
HLA-B27 positive [n = 150]	0 [0.0%]	1 [1.3%]	6 [9.7%]	0.15
Positive family for SpA	5 [38.5%]	20 [25.0%]	18 [29.0%]	0.59
Inflammatory back pain	5 [38.5%]	-	37 [59.7%]	0.001
Psoriasis[a]	2 [15.4%]	7 [8.8%]	5 [8.1%]	0.71
Dactylitis[a]	0 [0.0%]	1 [1.3%]	0 [0.0%]	0.62
Enthesitis[a]	0 [0.0%]	0 [0.0%]	1 [1.6%]	0.47
Uveitis[a]	1 [7.7%]	10 [12.5%]	9 [14.5%]	0.78
Preceding infection	0 [0.0%]	0 [0.0%]	0 [0.0%]	-
Alternating buttock pain	3 [23.1%]	0 [0.0%]	22 [35.5%]	0.001
Good response to NSAIDs [n = 44]	2 [15.4%]	20 [25.0%]	11 [17.7%]	0.57
Sacroiliitis on radiograph	1 [7.7%]	0 [0.0%]	4 [6.5%]	0.06
Sacroiliitis on MRI [n = 0]	-	-	-	-
Total SpA features, n [mean]	22 [1.7]	108 [1.4]	141 [2.3]	
Patients classified with SpA[b], n	6 [46.2%]	14 [17.5%]	43 [69.4%]	0.001
Elevated CRP, n	1 [7.7%]	15 [18.8%]	11 [17.7%]	0.64
Elevated ESR [n = 153], n	2 [15.4%]	26 [32.5%]	10 [16.1%]	0.60

SD, standard deviation; SpA, spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; MRI, magnetic resonance imaging; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

[a]All confirmed by a specialist.

[b]Based on one of the different SpA criteria.

diffuse idiopathic skeletal hyperostosis [DISH] of the lumbar spine. In total, 136/155 [87.7%] patients with self-reported joint/back pain were diagnosed with arthralgia. The mean BASDAI and mean BASFI of CBP patients were 3.1 [SD 1.9] and 2.2 [SD 1.9], respectively. The mean BASMI in pJTC patients with CBP was higher compared with pJTC patients without CBP: 1.7 [SD 0.9] vs. 1.4 [SD 0.8], $p = 0.03$.

Univariate analysis showed that CD [$p = 0.02$], female gender [$p = 0.001$], smoking [$p = 0.002$], IBD disease activity [$p < 0.001$], cutaneous manifestations [$p = 0.02$], and acute anterior uveitis [$p = 0.03$] were associated with an increased odds ratio [OR] for joint/back pain [Table 3]. In the multivariate analysis, the variables female gender (OR 1.97 [95% CI 1.10–3.53], $p = 0.02$), smoking (2.28 [95% CI 1.10–4.75], $p = 0.03$) and IBD disease activity (OR 4.07 [95% CI 2.23–7.45], $p < 0.001$ remained independently associated with IBD joint/back pain.

3.2. Classification

Overall, IBD patients with CBP had on average 1.7 SpA features, pJTC patients 1.4, and IBD patients with both CBP and pJTC had on average 2.3 different SpA features. Based on the various SpA features [Table 2], 155 patients with joint/back pain were classified according to the SpA criteria sets. In total, 28 out of the 155 patients [18.1%] conformed with more than one classification criteria set, and 63 [40.6%] patients fulfilled any of the SpA criteria sets: 32 [20.6%] patients fulfilled the Amor criteria, and 52 [33.5%] patients fulfilled the ESSG criteria, including 37 [71.2%] in the inflammatory back pain arm, 10 in the peripheral arm, and 5 in both arms. In all, 19 [12.3%] patients fulfilled the recently developed ASAS criteria, 6 met the axSpA criteria, and 15 met the pSpA criteria [Figure 2]. Four [2.6%] patients fulfilled the mNY criteria for AS. These four patients also fulfilled the Amor, the ESSG, and the ASAS criteria for axial SpA. There were no differences in gender and type of IBD between patients fulfilling any of the SpA criteria sets compared with those who did not fulfil any of the SpA criteria sets [data not shown].

3.3. Follow-up

In total, 242/255 [94.9%] patients were seen at the 12-month visit of the joint outpatient clinic [Figure 3]: 98 patients without and 144 patients with joint/back pain. Five of 98 patients without joint complaints at baseline developed joint complaints without symptoms or signs of disease activity, whereas 12 of 144 patients with joint complaints at baseline reported a cessation of joint/back pain at 12 months. Five of the 136 [3.7%] patients with arthralgia at Visit 1 developed arthritis, 1/136 [0.7%] developed enthesitis, and 1/136 [0.7%] developed tendinitis during the 12-month follow-up period.

A total of 245/255 [96.1%] patients completed all 12 questionnaires to assess IBD disease activity and spine and/or peripheral joint scores: 148/155 patients with and 97/100 patients without joint/back pain. A total of 122/148 [82.4%] IBD patients with joint/back pain completed ≥ 7 questionnaires in which they

Table 3. Logistic regression analyses of inflammatory bowel disease [IBD] patients, with the presence of arthropathies as the dependent variable.

Variable	*n*	Univariate		Multivariate	
		OR [95% CI]	*p*-Value	OR [95% CI]	*p*-Value
Age [years] Visit 1	255	1.0 [0.99–1.02]	0.71	-	
Gender					
Male [ref.]	97				
Female	158	2.47 [1.46–4.16]	0.001	1.97 [1.10–3.53]	0.02
Type of IBD					
UC [ref]	69				
CD	186	1.92 [1.10–3.36]	0.02	1.25 [0.66–2.35]	0.5
Smoking					
No [ref.]	195				
Yes	60	2.91 [1.48–5.73]	0.002	2.28 [1.10–4.75]	0.03
Active IBD disease[a]					
No [ref.]	153				
Yes	103	4.61 [2.57–8.26]	<0.001	4.07 [2.23–7.45]	<0.001
IBD-related surgery					
No [ref.]	148				
Yes	107	1.22 [0.73–2.04]	0.44	-	
Cutaneous manifestations[b]					
No [ref.]	221				
Yes	34	2.80 [1.17–6.71]	0.02	1.74 [0.66–4.56]	0.26
Ocular manifestation[c]					
No [ref.]	228				
Yes	27	3.14 [1.15–8.6]	0.03	1.83 [0.61–5.48]	0.28
Family history SpA[d]					
No [ref.]	181				
Yes	74	1.0 [0.57–1.74]	1.0	-	

OR, odds ratio; CI, confidence interval; UC, ulcerative colitits; CD, Crohn's disease; SpA, spondyloarthritis.

[a]Harvey-Bradshaw Index or Simple Clinical Colitis Activity Index score > 4.

[b]Cutaneous manifestations: psoriasis, erythema nodosum, pyoderma gangrenosum.

[c]Ocular manifestation: acute anterior uveitis.

[d]Family history SpA, ankylosing spondylitis, reactive arthritis, psoriasis, IBD, uveitis, all according to the definition of the ASAS criteria.

reported the course of their IBD disease activity and joint complaints in the 12-month follow-up. Of these 122 patients with joint/back pain in the follow-up period, IBD disease activity was continuously in clinical remission in 31.1% of patients, compared with 36.9% with continuous IBD disease activity and 32.0% with intermittent IBD disease activity. Smokers with CD appeared to be prone to developing continuous IBD disease activity, although the difference was not significant [p = 0.08]. In patients with joint/back pain, the HBI scores for general well-being [p = 0.002], abdominal pain [p = 0.025], diarrhoea [p < 0.001], aphthous ulcers [p = 0.03], and the SCCAI score on nocturnal pain [p < 0.001], all affected IBD disease activity compared with IBD patients in continuous clinical remission. Patients with continuous IBD disease activity were more likely to be referred to the rheumatologist [p = 0.04] for their joint complaints.

The linear mixed model analyses demonstrated that IBD disease activity was significantly associated with higher scores for disease activity of the spine, pain and nocturnal pain of the spine, disease activity of the peripheral joints, and pain and nocturnal pain of the peripheral joints, over time, with a range of regression coefficients estimated between 0.47–1.52 [all p < 0.05]. Thereafter, we also included type of IBD and gender as fixed factors. CD was only significantly associated with higher scores for pain and nocturnal pain of the peripheral joints [regression coefficients ranged 0.96–1.00, p < 0.05]. Gender had no significant effect.

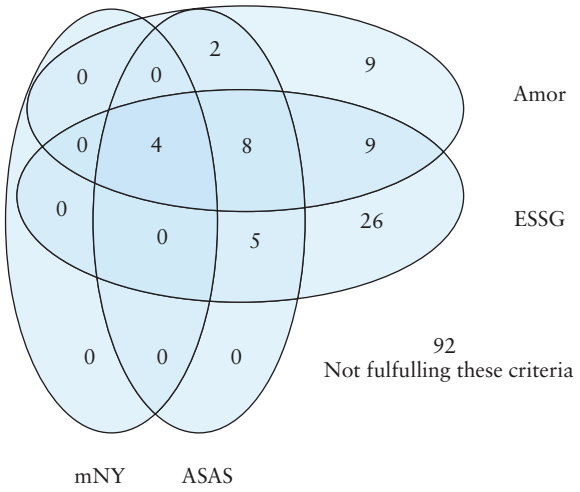

Figure 2. Venn diagram representing the overlap between the various classification criteria for SpA. Patients were classified as spondyloarthritis [SpA] according to the Amor,[15] European Spondyloarthropathy Study Group [ESSG],[16] Assessment of SpondyloArthritis international Society [ASAS] [axial and peripheral SpA],[17,18] and modified New York [mNY] criteria.[19]

4. Discussion

Since gastroenterologists are not used to the diagnosis and management of joint/back pain, a multidisciplinary approach in cooperation with rheumatologists is necessary.

In this prospective study, 255 IBD patients attended the multidisciplinary IBD JOINT outpatient clinic, including 155 with and 100 without joint/back pain. The patients in the former category reported joint pain, back pain, or both, and we characterised these complaints in depth. In our cohort, IBD patients reporting joint/back pain were more likely to be diagnosed with CD, female, smokers, and to show cutaneous manifestations and acute anterior uveitis, compared with patients without arthropathies. Female gender, smoking, and IBD disease activity were independently associated with joint/back pain in IBD. Moreover, IBD disease activity was significantly associated

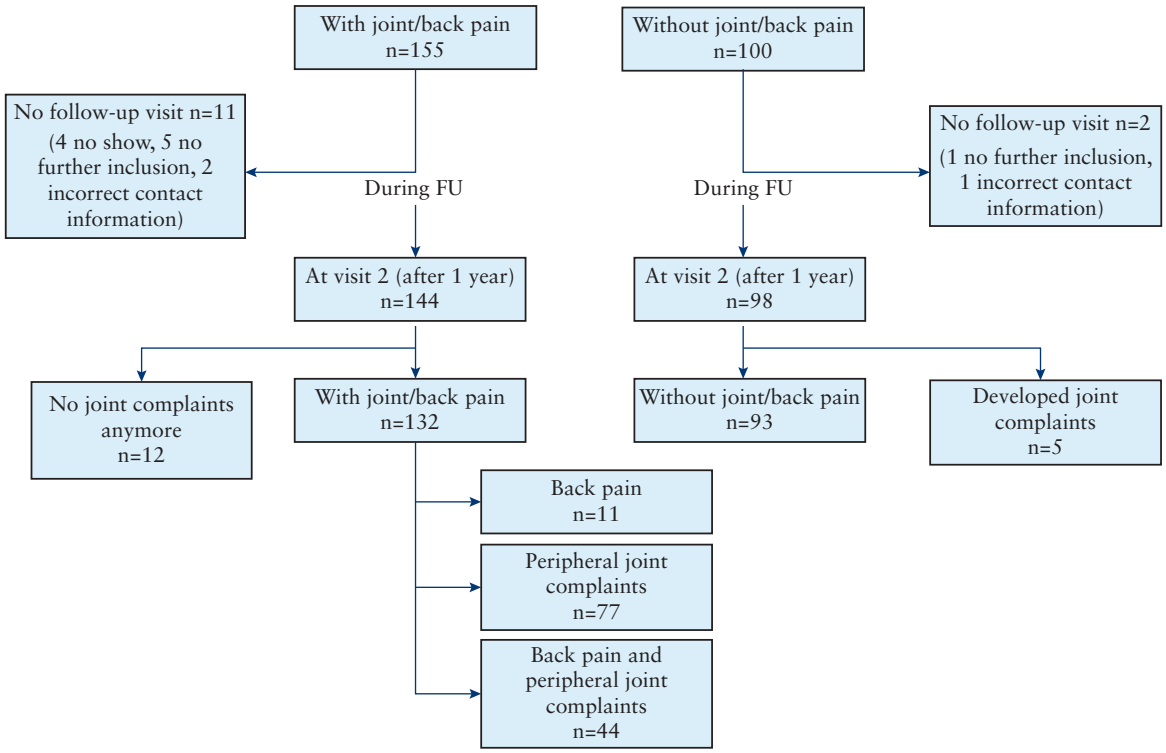

Figure 3. Follow-up inflammatory bowel disease [IBD] patients.

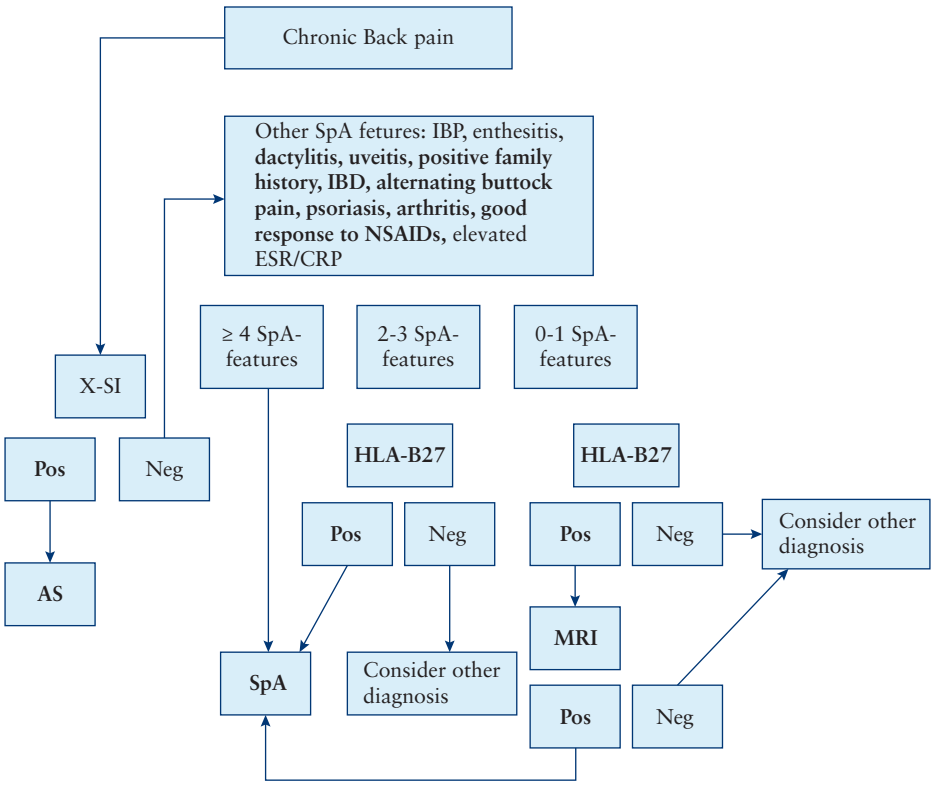

Figure 4. Proposal for the referral algorithm for suspected axial spondyloarthritis in patients with inflammatory bowel disease [IBD]. The first step for the gastroenterologist is to refer all patients with chronic back pain [CBP] to the radiologist to examine whether sacroiliitis can be found on the anterior-posterior [AP] plain radiograph of the pelvis. Conventional radiography of the sacroiliac [SI] joints is recommended as first imaging method but, in certain cases such as young patients and those with a short symptom duration, magnetic resonance imaging [MRI] is an alternative as first method.[38] The patients with an indicated sacroiliitis on the radiograph should be referred to the rheumatologist. In patients who are not positive for sacroiliitis of the pelvis, the presence of different SpA features should be ascertained. A patient with ≥ 4 SpA features should be referred to the rheumatologist and has a high probability of having axial SpA. Patients with fewer than four SpA features should undergo human leukocyte antigen –B27 [HLA-B27] testing. Patients with a positive HLA-B27 test and 2–3 SpA features possibly have axial SpA and thus will be referred to the rheumatologist. Patients with a positive HLA-B27 test and the presence of ≤ 1 SpA feature should undergo MRI.[31]

with pain and disease activity of the spine and peripheral joints over time. Although joint/back pain is frequently encountered in IBD patients,[1,2,3,14,20,21] only 12.3% fulfilled the ASAS criteria for SpA, which are most often used in clinical trials.[22] During the 12-month follow-up, the majority of patients showed no change in the presence or absence of joint/back pain. Based on an HBI or SCCAI score above 4, approximately 37% of the joint/back pain patients reported continuous IBD disease activity. A possible explanation for the high proportion described in previous studies[23,24,25] is that the bulk of the HBI score is due to diary card items [pain, diarrhoea, and general well-being]. Because the remaining index items [arthralgia, for example] make a proportionately smaller contribution, this may eventually lead to artificially elevated HBI scores. Van der Have *et al.* showed in this cohort that joint/back pain in IBD patients has a significant negative impact on quality of life [QoL] and work productivity. This difference remained significant during the follow-up of 12 months.[26]

Gastroenterologists should differentiate SpA patients from non-SpA patients, to make a distinction between the patients that should be referred to a rheumatologist and the patients that should remain under supervision of the gastroenterologist. This differentiation may be aided through the use of classification criteria based on the SpA features. Although classification criteria are not intended for use to diagnose SpA in clinical practice, the value of applying classification criteria is to distinguish typical cases of a particular disease using a standardised diagnostic process. Items in classification criteria reflect the essential features of a disease.[27]

Different SpA criteria were evaluated in this study and the finding that more patients complied with the ESSG criteria compared with the ASAS and Amor criteria can be attributed to the high number of IBD patients fulfilling the inflammatory back pain criteria according to the ESSG criteria set. Recent studies by van den Berg *et al.*[27,28] reported that the ASAS criteria for SpA outperformed the ESSG and Amor criteria. However, this is in contrast with the results described by Cheung *et al.*[29], where the ASAS criteria failed to perform better in comparison with the Amor and ESSG criteria. A possible explanation for these opposing results is the difference in disease duration in the described cohorts. The longer the disease duration, the more likely it is that symptoms develop.[30]

In our opinion, the ASAS criteria represent the most practical system with which to classify axial and peripheral SpA and are thus particularly applicable in the clinic because, based on this approach, all the subtypes of SpA will be recognised as distinct disease. In total, 12.3% of patients fulfilled the ASAS criteria for axial and peripheral SpA and should be referred to a rheumatologist. However, the number of patients classified as having axial SpA by the ASAS criteria is probably an underestimate in this study, because the axial SpA has not been proven by MRI.

Gastroenterologists need an efficient referral algorithm that can be applied to IBD patients with CBP. In total, 75 patients had CBP, although not all of them were suspicious for axial SpA. Based on the Berlin algorithm,[31] we propose a modified referral algorithm for IBD patients with suspected axial SpA, which can be utilised by gastroenterologists in the clinic to distinguish patients with a high probability of axial SpA from low-risk patients [Figure 4]. This proposed algorithm should be validated in future studies in an IBD cohort with joint/back pain.

Orchard *et al*. proposed the Oxford criteria for IBD patients with peripheral joint complaints. These criteria are often used by gastroenterologists, since they are unfamiliar with the diagnosis and management of joint/back pain in patients with IBD.[5] However, rather than using the Oxford criteria which mainly focus on peripheral joint complaints, joint/back pain in IBD patients is best categorised into SpA and non-SpA. This is also emphasised in our cohort, with only 15 patients [9.7%] fulfilling the Oxford criteria. Use of the Oxford criteria increases the chance that SpA patients with an axial component will be neglected.

Patients who do not fulfil the arthritis criteria can be classified as having arthralgia. Like most of the IBD patients with joint/back pain, these patients remain under the supervision of a gastroenterologist. As few gastroenterologists have the necessary expertise to correctly manage joint/back pain, an arthralgia treatment algorithm is also needed. Joint pain influences patient QoL and a better understanding of disease aetiology contributes to a better QoL.[26] Therefore, patients with arthralgia should be informed and educated about their symptoms. For example, smoking is independently associated with joint/back pain, thus patients should be aware that smoking increases the risk of development of joint complaints. Besides providing adequate information, effective interventions should be recommended. Physiotherapy is one intervention that can maintain or stimulate the flexibility of the joints without adverse effects. Studies have demonstrated the effectiveness of physiotherapy in patients with joint/back pain and the subsequent improvement of mobility of the joints.[32,33,34] Due to the common inflammatory pathways and the role of cytokines in IBD and arthropathies, IBD-related medication may also have a positive effect on joint complaints.[35]

We have shown that joint/back pain is correlated with IBD disease activity. Thus, a 'treat to target' strategy, including mucosal healing, could prove valuable in controlling symptoms of joint/back pain.[36,37] Future studies should evaluate the impact of mucosal healing on IBD-related joint/back pain.

In conclusion, proper classification and management of joint/back pain is a challenging task for gastroenterologists. Classification should be performed using existing rheumatological standards to further enhance multidisciplinary management in SpA-positive patients. Future approaches to IBD-associated joint/back pain should include care pathways guided by treatment algorithms applicable to the daily practice of the gastroenterologist.

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Conflict of Interest

HHF has acted as a consultant for Abbott. RAV has acted as a consultant for Abbvie, MSD, and Genzyme. AEM has acted as consultant for Abbvie, Ferring, and Dr Falk, and received payments for lectures from Abbvie and MSD.

Author Contributions

LKB, AEM, DWH: study concept and design. SJE, LKB, HHF, AEM, DWH: acquisition of data. SJE, LKB, FAG, DH, AEM, DWH: interpretation of data. SJE, LKB: drafting of manuscript. All authors: critical revision of the manuscript and final approval of the submitted manuscript. DWH: study supervision.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, de Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. *J Rheumatol* 2000;**27**:2860–65.
2. 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**:1307–13.
3. Palm Ø, Bernklev T, Moum B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health related quality of life. *J Rheumatol* 2005;**32**:1755–59.
4. Pizzi LT, Weston CM, Goldfarb NI, *et al*. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2006;**12**:47–52.
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. Dougados M, Baeten D. Spondyloarthritis. *Lancet* 2011;**377**:2217–37.
7. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, *et al*. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis* 2003;**62**:127–32.
8. Sieper J, Rudwaleit M, Baraliakos X, *et al*. The Assessment of SpondyloArthritis international Society [ASAS] handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;**68**[Suppl 2]:ii1–44.
9. van der Heijde D, Landewé R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index [BASMI] and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis* 2008;**67**:489–93.
10. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Callin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;**21**:2286–91.
11. Calin A, Garrett S, Whitelock H, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;**21**:2281–5.
12. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**8**:514.
13. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998;**43**:29–32.
14. Ruskin D, Lalloo C, Amaria K, *et al*. Assessing pain intensity in children with chronic pain: convergent and discriminant validity of the 0 to 10 numerical rating scale in clinical practice. *Pain Res Manag* 2014;**19**:141–8.
15. Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. *Rev Rheum Mal Osteoartic* 1990;**57**:85–9.
16. Dougados M, van der Linden S, Juhlin R, *et al*. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;**34**:1218–27.
17. Rudwaleit M, van der Heijde D, Landewé 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**:777–83.
18. Rudwaleit M, van der Heijde D, Landewé 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.
19. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;**27**:361–8.

20. Palm Ø, Moum B, Jahnsen J, Gran JT. 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**:1256–61.
21. Olivieri I, Cantini F, Castiglione F, *et al*. Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease. *Autoimmun Rev* 2014;**13**:822–30.
22. Raychaudhuri S, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. *J Autoimmun* 2014;**48–9**:128–33.
23. Khanna R, Zou G, D'Haens G, *et al*. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther* 2015;**41**:77–86.
24. Sandler RS, Jordan MC, Kupper LL. Development of a Crohn's index for survey research. *J Clin Epidemiol* 1988;**41**:451–8.
25. Thia K, Faubion WA Jr, Loftus EV Jr, Persson T, Sandborn WJ. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. *Inflamm Bowel Dis* 2011;**17**:105–11.
26. van der Have M, Brakenhoff LK, van Erp SJ, *et al*. Back/joint pain, illness perceptions and coping are important predictors of quality of life and work productivity in patients with inflammatory bowel disease: a 12-month longitudinal study. *J Crohns Colitis* 2015;**9**:276–83.
27. van den Berg R, de Hooge M, van Gaalen F, Reijnierse M, Huizinga T, van der Heijde D. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early [SPACE] cohort. *Rheumatology [Oxford]* 2013;**52**:1492–9.
28. van den Berg R, van Gaalen F, van der Helm-van Mill A, Huizinga T, van der Heijde D. Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis cohort. *Ann Rheum Dis* 2012;**71**:1366–9.
29. 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 Spondylarthropathy Study Group. *J Rheumatol* 2012;**39**:816–21.
30. Molto A, Paternotte S, Comet D, *et al*. Performances of the ASAS Axial Spondyloarthritis criteria for diagnosis and classification purposes in patients visiting a rheumatologist because of chronic back pain: The Declic study. *Arthritis Care Res* 2013;**65**:1472–81.
31. 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**:1646–53.
32. Stenström CH, Minor M. Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. *Arthritis Rheum* 2003;**49**:428–34.
33. Häkkinen A, Sokka T, Hannonen P. A home-based two-year strength training period in early rheumatoid arthritis led to good long-term compliance: a five year follow-up. *Arthritis Rheum* 2004a;**51**:56–62.
34. Häkkinen A, Sokka T, Kautainen H, Kotaniemi A, Hannonen P. Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a five year follow-up. *Ann Rheum Dis* 2004b;**63**:910–6.
35. Wendling D, Vuitton L, Koch S, Prati C. Spondyloarthritis and the gut: A new look. *Joint Bone Spine* 2015;**82**:779.
36. Bouguen G, Levesque BG, Feagan BG, *et al*. Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease. *Clin Gastroenterol Hepatol* 2015;**82**:77–9.
37. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent [erosive] arthritis. *Arthritis Rheum* 2002;**46**:357–65.
38. Mandl P, Navarro-Compán V, Terslev L, *et al*; European League Against Rheumatism [EULAR]. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015;**74**:1327–39.