**Ankylosing Spondylitis and Axial Spondyloarthritis in Patients with Inflammatory Bowel Disease: Results From 20 years of Follow-up in the IBSEN Study**

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**Abstract**

Background and aims: Patients with inflammatory bowel disease (IBD) often suffer from rheumatic manifestations, including inflammatory back disorders. The prevalence of these disorders late in the course of IBD is poorly investigated. The aim of this study was to estimate the prevalence of inflammatory back disorders in patients with IBD 20 years after diagnosis, to investigate possible associations with IBD severity as well as HLA-B27, and the NOD2 genotype.

Methods: A population-based cohort (the IBSEN study) was followed prospectively for 20 years. Information covering IBD activity and rheumatic diseases was collected at the regular follow-ups. HLA-B27 and NOD2 were analysed as present or absent.

Results: At 20 years, 599 of the original cohort were alive, of whom 470 (78.5 %) were investigated (314 ulcerative colitis and 156 Crohn’s disease patients). Ankylosing spondylitis was diagnosed in 21 patients (4.5 %), axial spondyloarthritis was diagnosed in 36 patients (7.7 %), and inflammatory back pain was diagnosed in 54 patients (11.5 %). Chronic back pain (back pain > 3 months) was present in 220 patients (46.8 %). HLA-B27 was associated with ankylosing spondylitis, axial spondyloarthritis, and inflammatory back pain, whereas no significant association was found for NOD2. A more chronic IBD course was associated with axial spondyloarthritis.

Conclusion: Our data revealed a high prevalence of ankylosing spondylitis, axial spondyloarthritis, and inflammatory back pain 20 years after IBD diagnosis. HLA-B27 but not NOD-2 was a predisposing factor for the inflammatory back disorders in IBD. Axial spondyloarthritis was associated with a more chronic active IBD disease course.

Keywords: inflammatory bowel disease, ankylosing spondylitis, axial spondyloarthritis, extraintestinal manifestations

**Introduction**

Patients with inflammatory bowel disease (IBD) frequently suffer from extraintestinal symptoms (1). The most common symptoms are musculoskeletal manifestations, which are usually classified as spondyloarthritis (SpA).

SpA can be subgrouped according to the clinical presentation with either predominantly axial manifestations or peripheral arthritis (2). The term axial spondyloarthritis (axial SpA) covers the patients with mainly axial (spinal) manifestations, including patients with ankylosing spondylitis (formerly known as Bechterew’s disease) (3). Inflammatory back pain is one of the characteristics that defines axial SpA and is also one of the earliest symptoms (4). Inflammatory back pain is distinguished from non-inflammatory back pain by certain characteristics, such as an insidious onset and improvement with exercise, although the accuracy of these characteristics has been debated (5).

Gastroenterologists are often the first physicians to meet patients with these musculoskeletal manifestations due to their associations with IBD (6). Early diagnosis of axial SpA is important because delay of treatment can lead to more severe disease development (7, 8). Low back pain is a common condition (9), and simple criteria can distinguish inflammatory back pain from non-inflammatory back pain(2) and consequently enable recognition of patients at risk of developing axial SpA and ankylosing spondylitis.

The overall prevalence of SpA in IBD patients has been reported to range from 17 % to 39 % (10). This wide range is partially explained by differences in the IBD duration, age and gender distributions, differences in diagnostic criteria and geographical regions. Genetic predispositions for the development of SpA and sacroiliitis have been documented, and a striking correlation between the presence of human leukocyte antigen (HLA-B27) and SpA has been found. The prevalence of HLA-B27 in populations has been associated with geographical areas and is relatively high in northern countries (11). Nucleotide-binding oligomerisation domain 2 (NOD2) increases the risk of Crohn’s disease and has also been linked to radiographic sacroiliitis in IBD patients (12).

The onset of SpA symptoms usually occurs before the age of 50 (13), and most patients present with symptoms early in the IBD course; in some cases these symptoms are diagnosed prior to the intestinal disease (14). However, late onset ankylosing spondylitis and SpA are also observed, and their incidence rates are expected to increase in coming years (15). Studies estimating the prevalence of SpA (including ankylosing spondylitis) in IBD patients late in the disease course are rare, and population-based data are missing (6).

The primary aim of this study was to determine the prevalence of inflammatory back disorders in IBD patients 20 years after diagnosis. The secondary aim was to investigate possible associations between back disorders and the IBD severity, HLA-B27 presence and NOD2 genotype.

**Methods**

**Patients and study design**

The Inflammatory Bowel South-Eastern Norway (IBSEN) study included all newly diagnosed cases of IBD in four well-defined areas in southeastern Norway (Oslo, Østfold, Telemark and Aust-Agder counties) from 1 January 1990 to 31 December 1993. The diagnosis was made according to the internationally accepted Lennard-Jones criteria (16). Detailed information regarding the cohort has been described elsewhere (17, 18). Scheduled follow-ups were conducted 1, 5, 10 and 20 years after inclusion with a clinical examination, structured interview, laboratory tests and colonoscopies. At the 5-year follow-up, the patients who gave informed consent underwent a rheumatological assessment. This assessment included a structured interview covering the symptoms of back disorders, examination by a rheumatologist, and radiography of the thoracolumbar spine and sacroiliac joints by plain X-ray or computed tomography. Details regarding methods and results have been published elsewhere (19). At the 20-year follow-up, all patients were asked to complete a self-administered questionnaire with detailed questions regarding the course of their IBD disease, symptoms of inflammatory back disorders and rheumatic diseases diagnosed by a physician. The questionnaire covered rheumatological features investigated at the 5-year follow-up and updated information for the classification of back disorders.

**Diagnostic criteria of back disorders**

Axial SpA was diagnosed according to the Assessment of Spondyloarthritis International Society (ASAS) criteria (2) and inflammatory back pain was diagnosed according to the ASAS (2) and Calin criteria (20) (Figure 1 and Table 1).



Figure 1. The Assessment of Spondyloarthritis International Society (ASAS) classification criteria for Axial Spondyloarthritis (2).

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| --- | --- | --- |
| **Inflammatory back pain criteria** | **ASAS: 4 out of 5** | **Calin et al.: 4 out of 5** |
| Duration of back pain (>3 months) |  | √ |
| Morning stiffness |  | √ |
| Insidious onset of back pain | √ | √ |
| Age at onset of back pain < 40 years | √ | √ |
| Pain improves with exercise/activity | √ | √ |
| Pain at night | √ |  |
| No improvement with rest\* | √ |  |

Table 1. Criteria for inflammatory back pain according to The Assessment of Spondyloarthritis International Society (ASAS) (2) and Calin et al. (20). \*Not part of our questionnaire at 5-year follow-up, only examined at the 20-year assessments.

Data from the previous 5-year follow-up and the detailed questionnaire at the 20-year follow-up enabled us to identify patients who fulfilled these criteria. The diagnosis-making process was supervised by a rheumatologist. The diagnosis of ankylosing spondylitis followed the modified New York criteria (21) and was based on the rheumatological investigation at the 5-year follow-up visit, including the disease history, clinical investigation and radiographic assessment of the sacroiliac joints (19). Additional cases of ankylosing spondylitis diagnosed between the 5-year and 20-year follow-ups had to be diagnosed by a physician according to the patients’ questionnaires. For ankylosing spondylitis, axial SpA, and chronic back pain, the numbers of cases were added from the follow-ups at 5 and 20 years.

The questionnaire at the 5-year follow-up included the Calin criteria for inflammatory back pain (20). These criteria overlapped with the ASAS criteria (Table 1). One item of the ASAS criteria was not part of the 5-year follow-up questionnaire, due to minor differences between the criteria. Four items were necessary to fulfil the diagnosis of inflammatory back pain in both sets of criteria. The patients registered with inflammatory back pain fulfilled either the ASAS or Calin criteria and represented the accumulated numbers from the 5- and 20-year follow-ups.

Chronic back pain (including non-inflammatory and inflammatory back pain) was defined as persistent back pain for a period of at least three consecutive months.

**IBD severity**

The IBD severity was assessed by the ulcerative colitis (UC) extent and Crohn’s disease (CD) location and behaviour (both according to the Montreal criteria), the IBD activity curves, and medication use. The clinical course of IBD from diagnosis onward was presented in four predefined curves (Figure 4). Each curve reflected a different pattern of the disease course from the patient’s perspective (18).

For the purpose of the statistical analysis, curve number 2 (initially low activity followed by an increase in the severity of the intestinal symptoms) was left out of our calculations due to the low numbers in this group. Curves 3 and 4 were combined in the analyses and called chronic persistent or intermittent activity.

**HLA-B27 and NOD2**

HLA-B27 analyses were registered as positive (HLA-B27 present) or negative (absent). NOD2 was genotyped for three single nucleotide polymorphisms in the NOD2 gene known to be associated with CD. Detailed descriptions are given elsewhere (22).

**Magnetic resonance imaging (MRI) and sacroiliac joint assessment**

As part of the 20-year follow-up assessment, all patients with CD were offered standard magnetic resonance imaging (MRI) (see Appendix) of their small intestine. This investigation also visualised the sacroiliac joints (23, 24) and enabled the diagnosis of radiographic axial SpA according to the ASAS 2016 criteria for MRI (25). Two experienced radiologists analysed the images independently, and diagnostic disagreements were resolved by consensus reading when the final diagnosis was decided. The reviewers were blinded to previous imaging findings and other clinical data except that the patients were part of the IBSEN 20-year follow-up.

**Statistical analysis**

Continuous variables were described with the median and range, and categorical variables were described with counts and percentages. Crude comparisons between pairs of categorical data were performed using the chi-square test or Fisher’s exact test when appropriate.Crude comparisons between groups regarding continuous variables were performed using non-parametric methods, such as the Kruskall-Wallis test. All tests were two-sided. Due to the exploratory nature of our analyses and to correct for multiple testing, p-values ≤0.01 were considered statistically significant. All analyses were performed using SPSS version 24.

**Results**

**Cohort and baseline demographics**

Twenty years after the IBD diagnosis, 599 patients from the original population-based cohort of 756 patients were alive. Of these patients, 470 (78.5 %) underwent a clinical follow-up (Figure 2). The completion rate for questionnaires regarding rheumatic symptoms and diagnoses was 94 % in the UC patients and 93 % in the CD patients. Of the 441 patients who answered the questionnaire, 365 were part of the rheumatic investigations at the 5-year follow-up. The demographics and IBD characteristics for the patients answering the questionnaire are listed in Table 2. No significant differences in gender, age, current smoking status, UC extent, CD location, behaviour, or perianal disease were found between the patients who answered or did not answer the rheumatic questionnaire.



Figure 2. Flow chart of the participants at inclusion and the 20-year follow-up, illustrating those lost to follow-up or dead. UC, ulcerative colitis; CD, Crohn’s disease.

**Table 2. Patient demographics and IBD characteristics at the 20-year follow-up**

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| --- | --- | --- |
|  | **Ulcerative colitis**  **n=296**  **n (%)** | **Crohn’s disease**  **n=145**  **n (%)** |
| Females | 152 (51.4) | 73 (50.3) |
| Age, median (range) | 53.4 (29.5 – 86.1) | 47.8 (27.4 - 94.0) |
| Current smoking status  *Missing = 5* | 43 (14.5) | 41 (28.3) |
| UC extent |  |  |
| Proctitis | 53 (17.9) |  |
| Left-sided | 98 (33.1) |  |
| Extensive colitis | 145 (49.0) |  |
| CD location |  |  |
| Ileal |  | 22 (15.2) |
| Colonic |  | 41 (28.3) |
| Ileocolonic |  | 82 (56.6) |
| Upper  *Missing = 5* |  | 1 (0.7) |
| CD behaviour |  |  |
| Non-stricturing,  non-penetrating |  | 54 (37.2) |
| Stricturing |  | 46 (31.7) |
| Penetrating |  | 45 (31.0) |
| Perianal disease  *Missing = 4* |  | 18 (12.4) |

Table 2. Description of the participants who answered the rheumatic questionnaire at the 20-year follow-up based on demographics and inflammatory bowel disease (IBD) characteristics. The ulcerative colitis (UC) extent is the maximal extent during the entire follow-up period. The Crohn’s disease (CD) location and behaviour are based on the maximal Montreal classification for the entire follow-up period.

**Back disorders**

Ankylosing spondylitis was diagnosed in 21 patients (4.5 %) with IBD. Eight of these were not diagnosed at the 5-year follow-up (seven UC and one CD), whereas one patient with ankylosing spondylitis at the 20-year follow-up did not participate in the rheumatological investigation at the 5-year time point. Axial SpA was diagnosed in 36 patients (7.7 %), of whom 21 fulfilled the diagnostic criteria at the 5-year follow-up. Inflammatory back pain occurred during the disease course in 54 patients (11.5 %) according to the ASAS (2) and in 105 patients (22.3 %, 65 UC and 40 CD) according to the Calin criteria (20). Twenty-one patients (4.5 %) had ongoing symptoms of inflammatory back pain according to the ASAS criteria over the three months preceding the 20-year follow-up. Chronic back pain (non-inflammatory and inflammatory) was present at some time during the 20-year observation period in 220 patients (46.8 %) (Figure 3).



Figure 3. Back disorders in the IBSEN cohort at the 20-year follow-up. Inflammatory back pain was diagnosed according to the ASAS criteria (2). No significant differences between the ulcerative colitis (UC) and Crohn’s disease (CD) patients were found. IBD, inflammatory bowel disease; ASAS, Assessment of Spondyloarthritis International Society.

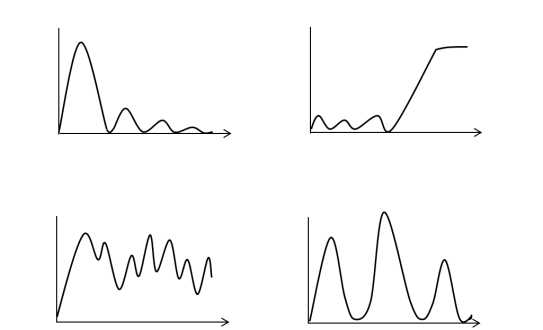


Figure. 4. Predefined inflammatory bowel disease (IBD) activity curves from the IBSEN study. Top left: Curve 1: Initially highly active disease followed by remission or mild symptoms. Top right: Curve 2: Initially low activity followed by an increase in the severity of intestinal symptoms. Bottom left: Curve 3: Chronic continuous symptoms. Bottom right: Curve 4: Chronic intermittent symptoms.

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|  | **Chronic back pain**  **n=220**  **n (%)** | **Inflammatory back pain**  **(ASAS)**  **n=54**  **n (%)** | **Axial spondylo-arthritis**  **n=36**  **n (%)** | **Ankylosingspondylitis**  **n=21**  **n (%)** | **Patients without back complaints**  **n=242**  **n (%)** |
| **Females** | 129 (58.6)\* | 35 (64.8)\* | 17 (47.2) | 8 (38.1) | 102 (42.1) |
| **Age, median (range)** | 53.7  (27.4 -85.2)\* | 51.1  (36.6 -72.2) | 50.0 (32.7 -85.2) | 52.4  (32.6 -83.2) | 48.8  (28.8 -94.0) |
| **UC (n = 314)** | 145 (46.2) | 31 (9.9) | 19 (6.1) | 13 (4.1) | 164 (52.2) |
| **UC extent** |  |  |  |  |  |
| **Proctitis/left-sided** | 76 (52.4) | 18 (58.1) | 10 (52.6) | 6 (46.2) | 80 (48.8) |
| **Extensive colitis** | 69 (47.6) | 13 (41.9) | 9 (47.4) | 7 (53.8) | 84 (51.2) |
| **UC onset <40 years** | 92 (63.4) | 22 (71.0) | 13 (68.4) | 8 (61.5) | 118 (72.0) |
| **CD (n = 156)** | 75 (48.1) | 23 (14.7) | 17 (10.9) | 8 (5.1) | 78 (50.0) |
| **CD onset <40 years** | 54 (72.0)\* | 21 (91.3) | 14 (82.4) | 7 (87.5) | 69 (88.5) |
| **CD location** |  |  |  |  |  |
| **Ileal** | 10 (13.3) | 3 (13.0) | 2 (11.8) | 0 | 13 (16.7) |
| **Colonic** | 21 (28.0) | 6 (26.1) | 3 (17.6) | 1 (12.5) | 22 (28.2) |
| **Ileocolonic** | 44 (58.7) | 14 (60.9) | 12 (70.6) | 7 (87.5) | 43 (55.1) |
| **CD behaviour** |  |  |  |  |  |
| **Non-stricturing,**  **non-penetrating** | 35 (46.7)\* | 9 (39.1) | 7 (41.2) | 5 (62.5) | 21 (26.9) |
| **Stricturing/ penetrating** | 40 (53.3)\* | 14 (60.9) | 10 (58.8) | 3 (37.5) | 57 (73.1) |
| **IBD activity curves** |  |  |  |  |  |
| **C1** | 137 (62.3) | 28 (51.9) | 16 (44.4)\* | 10 (47.6) | 168 (69.4) |
| **C3/C4** | 68 (30.9) | 20 (37.0) | 16 (44.4)\* | 8 (38.1) | 67 (27.7) |
| **Medication ever used** |  |  |  |  |  |
| **Corticosteroids** | 130 (59.1) | 37 (68.5) | 24 (66.7) | 14 (66.7) | 139 (57.4) |
| **Biological** | 22 (10.0) | 9 (16.7) | 6 (16.7) | 3 (14.3) | 23 (9.5) |
| **Immunomodulators** | 51 (23.2) | 16 (29.6) | 13 (36.1) | 7 (33.3) | 61 (25.2) |
| **HLA-B27 positive** | 30 (13.6) | 14 (25.9)\* | 25 (69.4)\* | 12 (57.1)\* | 17 (7.0) |
| **NOD 2** | 12 (5.5) | 2 (3.7) | 0 | 0 | 13 (5.4) |

Table 3. Disease characteristics for patients with and without back disorders at the 20-year follow-up.

The ulcerative colitis (UC) extent was the maximal extent during the entire follow-up period. The Crohn’s disease (CD) location and behaviour were based on the maximal Montreal classification for the entire follow-up period. Inflammatory bowel disease (IBD) activity curves for the entire follow-up period were as follows: C1: initially highly active disease followed by remission or mild symptoms; C3: chronic persistent activity; C4: chronic intermittent activity (C3 and C4 were combined into one group). Medication is defined as having ever used medication during the 20-year follow-up. Immunomodulators include azathioprine and methotrexate. HLA-B27, human leukocyte antigen; NOD2, nucleotide-binding oligomerisation domain 2; ASAS, Assessment of Spondyloarthritis International Society.

\* Significant (p≤0.01), compared with the patients without any back complaints.

**Magnetic resonance imaging (MRI)**

MRI of the small intestine and the sacroiliac joints was performed in 96 of the 156 CD patients (62 %).One MRI result was excluded due to poor imaging quality. The statistical analysis showed no significant differences in disease activity, disease behaviour or disease location between the patients with or without a performed MRI (data not shown). The MRI evaluations detected 14 patients with sacroiliitis (14.7 %), of whom 10 patients had active sacroiliitis as defined by ASAS 2016 (25). Two of the patients with active sacroiliitis were previously diagnosed with ankylosing spondylitis and thus had already fulfilled the diagnostic criteria for axial SpA. Six of the patients with active sacroiliitis did not fulfil the criteria for axial SpA, of whom five were asymptomatic and one had onset of back pain after the age of 45 years. Thus, asymptomatic active sacroiliitis was found in 5/95 (5.3 %) patients with CD.

**IBD severity**

Significantly more patients with axial SpA reported chronicity in their IBD course according to the predefined IBD activity curves (Figure 4) than the patients without back complaints (Table 3). No significant differences were found between the UC and CD patients.

The UC extent, CD location and behaviour (according to the Montreal classification), and medication received during follow-up were not significantly different between the patients with back disorders and those without back complaints. The patients with chronic back pain differed significantly from those without back complaints, with a later IBD onset and a greater proportion of women in the group with chronic back pain (Table 3).

**HLA-B27 and NOD2**

The HLA-B27 prevalence was 10.2 % among all IBD participants at the 20-year follow-up and was significantly more prevalent among the patients with ankylosing spondylitis, axial SpA, and inflammatory back pain than among the patients without back complaints (Table 3). The prevalence of the NOD2 gene polymorphisms was 9.1 % (13/314) among the CD patients and 4.1 % (14/156) among the UC patients, which did not represent a significant difference between the diagnoses. NOD2 was not associated with any of the investigated back disorders, including the group of CD patients with asymptomatic sacroiliitis.

**Discussion**

Twenty years after the IBD diagnosis, the prevalence of ankylosing spondylitis was 4.5 %, axial SpA was 7.7%, of inflammatory back pain according to ASAS was 11.5 %, and of chronic back pain was 46.8 %. No significant differences were found between the UC and CD patients. Patient-reported chronicity of intestinal symptoms was associated with a higher prevalence of axial SpA. The presence of HLA-B27 was associated with an increased occurrence of inflammatory back pain, axial SpA, and ankylosing spondylitis. NOD2 was not associated with radiological sacroiliitis or the other investigated back disorders.

**Ankylosing Spondylitis**

The association between ankylosing spondylitis and IBD was previously documented (26), and a higher prevalence among IBD patients than in the general population was as expected. The prevalence of ankylosing spondylitis in the general population has been estimated as 0.26 % in northern Norway (27) and 0.25 % in Europe (28). The prevalence of ankylosing spondylitis in our study was 13-18 times higher than these results.

The prevalence of ankylosing spondylitis among the IBD patients was 3 % in a meta-analysis by Karreman et al (6); this analysis included 43 studies, most of which were retrospective and cross-sectional studies, but also included some prospective follow-up studies. The heterogeneity in this analysis was high, with the greatest variability related to geographical differences and a higher prevalence in Europe and North America, where the susceptibility factor HLA-B27 is more prevalent than in southern regions (28). The included studies also differed by the selection of patients and the classification criteria applied for the diagnosis, which might also explain the lower prevalence compared with our results.

Van Erp et al. (29) found a prevalence of ankylosing spondylitis among IBD patients of 1.6 % according to the modified New York criteria (21). This lower prevalence of ankylosing spondylitis might be due to a lower HLA-B27 prevalence, which was 9.7 % in the subgroup of their patients with joint/back pain compared with the 13.6 % prevalence in our patients with back pain. Additionally, the shorter follow-up time and IBD duration could have contributed to the differences in the prevalence. In a Swiss population-based study of IBD patients (30), 4.1 % had ankylosing spondylitis, which was slightly lower than the prevalence in our study. In the Swiss study, the patients underwent a clinical assessment and questionnaire that were similar to our study design. D’Inca et al. (31) found a lower prevalence of ankylosing spondylitis of 1.4 % among IBD patients in Italy visiting an outpatient clinic over a 12-month period. Their lower prevalence can be explained partly by the inclusion of only patients with ongoing symptoms in the rheumatological evaluation. Karmiris et al. (32) found a prevalence of 2.1 % among 1860 IBD patients in Greece. Their data were collected retrospectively; thus, cases might have been overlooked, which could have contributed to the lower prevalence of ankylosing spondylitis compared with our results.

The prevalence of ankylosing spondylitis among our patients increased from 3.7 % (n = 15) after the 5-year follow-up (19) to 4.5 % (n = 21) at the 20-year follow-up. Consequently, most cases were diagnosed within five years from the IBD diagnosis. Of the patients diagnosed with ankylosing spondylitis at the 5-year follow-up, two failed to report this at the 20-year follow-up questionnaire. Most of the patients (7/8) diagnosed later than 5 years from the IBD diagnosis had UC. Although the symptoms of ankylosing spondylitis may present early, typically sacroiliitis is not visible on X-ray (which was used at the 5-year follow-up), and a proper diagnosis may be delayed for several years (33). This phenomenon can partially explain the higher prevalence of ankylosing spondylitis at the 20-year follow-up compared with the 5-year follow-up, but we have no explanation for the predominance of UC with late onset ankylosing spondylitis.

**Axial spondyloarthritis (axial SpA)**

Visible sacroiliitis on an X-ray or computed tomography are necessary for the diagnosis of ankylosing spondylitis according to the modified New York criteria, but these findings occur quite late in the disease course. This issue led to the development of the ASAS classification criteria in 2009 (2), which attempted to detect cases earlier and distinguish between axial and peripheral SpA (34, 35). The association between SpA and gut inflammation has been known for a long time (36). Van Praet et al. examined 65 patients with SpA, of which 49 had axial SpA, and found that 46.2 % showed microscopic gut inflammation with a strong similarity between the microscopic and macroscopic findings (36). Despite the prevalent intestinal inflammation, only approximately 5 % of the 217 SpA patients developed IBD within their disease evolution of 2-9 years (37).

The prevalence of axial SpA was similar in the UC and CD patients but was higher than previously reported. In the Netherlands, Stolwijk et al. (38) found a prevalence of 5.1 % in the South Limburg cohort, and Van Erp et al. (29) reported a prevalence of 2.4 % among IBD patients in an outpatient clinic. The study by Stolwijk et al. estimated the prevalence of axial SpA only in patients visiting a rheumatologist, which accounted for approximately half of the patients with musculoskeletal SpA features. Both studies had a maximum observation time of one year and mean IBD durations of only approximately 11 years (38) and 15 years (29), respectively. These differences may have contributed to the lower prevalence compared with our study.

**Inflammatory back pain**

Inflammatory back pain is one defining characteristic of ankylosing spondylitis and SpA (39). Sets of criteria defining inflammatory back pain have been developed over the past 40 years. The first set of criteria was developed in 1977 by Calin et al. (20), which we used at the 5-year follow-up. In the current 20-year follow-up study, we applied both the Calin and the ASAS criteria (2), with a main focus on the latter criteria which have been used most often together with the axial SpA criteria since 2009 (2).

The prevalence of inflammatory back pain in our cohort was 11.5 % according to the ASAS and 22.3 % according to the less stringent Calin criteria. In Norfolk in the UK, a cross-sectional cohort study performed in a large general practice (40) estimated a prevalence of inflammatory back pain in the primary care population of 1.7 % using the ASAS criteria and 3.0 % using the less strict Calin criteria. The NHANES survey (National Health and Nutrition Examination Survey) in the USA showed a prevalence of inflammatory back pain according to the Calin criteria of 5.0 % (41). The ASAS criteria were not applied in the study.

Among patients with IBD, Stolwijk et al. reported a prevalence of inflammatory back pain of 22.6 % (79/350) (38). Their definition of inflammatory back pain was almost identical to the Calin criteria, and the prevalence was comparable to our study. Thus, inflammatory back pain occurs in more than one out of five patients with IBD and is clearly more prevalent than in the general population.

**Chronic back pain**

Almost half of the patients in our study reported having ever experienced chronic back pain. This percentage was higher than expected in the general Norwegian population (20-33 %) (42, 43). A worldwide systematic review from 2015 showed an overall chronic low-back pain prevalence of 23.3 % in individuals aged 25 to 74 and 25.4 % among older adults (> 60 years old) (44). Chronic back pain is a nonspecific symptom with many different causes. Our data support a higher prevalence among patients with IBD than is expected in the general population.

**IBD severity**

We found that patients reporting persistent or relapsing intestinal disease activity over a 20-year IBD course (disease curves 3 and 4, Figure 4) seemed to be more prone to developing axial SpA. This finding is somewhat unexpected, because SpA is believed to progress independently of the intestinal disease activity (45). Vavricka et al. (30) did not find any association between IBD activity (Crohn’s Disease Activity Index (CDAI) for CD activity and the Truelowe-Witts severity index for UC) and the prevalence of ankylosing spondylitis. However, Van Erp et al. (29) reported an association between patients with chronic back pain/joint pain and IBD activity, using the Harvey-Bradshaw index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI) score > 4. We did not find an association between any of the back disorders and the HBI or SCCAI scoring indices at the 20-year follow-up (calculations not shown). However, these scoring tools are unsuitable for investigating the development of back disorders over a 20-year time period, since they only provide a snapshot impression of the disease course. Conversely, the IBD activity curves reflect the entire disease course. IBD severity can also be classified by the UC extent or CD localisation and behaviour, according to the Vienna or Montreal classifications or by the need for medication. Karmiris et al. (32) reported an association between the prevalence of ankylosing spondylitis and worsening of CD behaviour in a retrospective study in Greece, but we found no association with the given back disorders and CD behaviour in our study (Table 3).

**HLA-B27 and NOD2**

The prevalence of HLA-B27 among our IBD patients with ankylosing spondylitis was 57.1 %, which was lower than the prevalence in idiopathic ankylosing spondylitis (12) but clearly confirmed that HLA-B27 is a predisposing factor for ankylosing spondylitis and axial SpA (46). The quite high frequency of HLA-B27 in the Norwegian population and among our patients probably contributed to a higher prevalence of ankylosing spondylitis and axial SpA (11). Previous studies have linked NOD2 to radiographic sacroiliitis in IBD patients but not to idiopathic ankylosing spondylitis or SpA (12). We found no such associations among our patients.

**Strengths and limitations**

One of the strengths of this study is the design based on a prospective population-based cohort with long-term follow-up. Information was gathered through regular controls and with high completeness. Moreover, the Norwegian health care system is available to all Norwegian citizens, which enabled a high and reliable inclusion rate in the study. Therefore, the IBSEN study represents an important population-based IBD cohort.

Among the limitations of this study was that the MRI was conducted in only 96 of the patients with CD. Therefore, sacroiliitis might have been overlooked among some of the patients who were not systematically investigated. A systematic rheumatological questionnaire assessment was performed at the 20-year follow-up, but an additional clinical investigation by a rheumatologist would have been superior, at the 20-year follow-up and the former follow-ups. The possibility of recall bias cannot be excluded, and cases might have been overlooked. A missing question for the ASAS inflammatory back disease criteria could have contributed to a smaller underestimation of the prevalence. Given the limited sample sizes, we were not able to fit more advanced statistical models into our study.

Few patients in our study received biological medication, and those who were administered such medication received it late in the disease course. Tumor necrosis factor (TNF)-α inhibitors, which currently are more often used in clinical caretaking for IBD, are efficient in the treatment of both axial SpA and ankylosing spondylitis (7). This treatment of IBD patients may mask the symptoms of these conditions in some patients and thereby lead to underestimation of the prevalence.

**Conclusion**

In this population-based IBD cohort followed for 20 years after diagnosis, we observed a high prevalence of ankylosing spondylitis, axial SpA, and inflammatory back pain. The prevalence of ankylosing spondylitis had increased since the 5-year follow-up. HLA-B27 but not the NOD2 genotype was a predisposing factor for inflammatory back disorders in IBD patients. Patient-reported chronic persistent or relapsing IBD activity was associated with a higher prevalence of axial SpA, whereas no other phenotypic factors were associated with inflammatory back disorders in this study.

**Conflict of interest**

MLH has received lecture fees from Takeda, MSD, Meda, and Abbvie.

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**Author contributions**

The authors have contributed to the following:

The conception and design of the study: AO, ØP, BM and MLH.

Acquisition of data: AO, ØP, AKL, HB, AN, MH, OH, BM and MLH.

Interpreting data: AO, ØP, MC, BM and MLH.

Statistical analysis: AO and MC.

Drafting the manuscript: AO, ØP, AKL, MC, BM and MLH.

Final approval of the submitted manuscript: AO, ØP, AKL, MC, HB, AN, OH, MH, BM and MLH.

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