Non-Inflammatory Joint Pain in Patients with Inflammatory Bowel Disease Is Prevalent and Has a Significant Impact on Health Related Quality of Life

ØYVIND PALM, TOMM BERNKLEV, BJØRN MOUM, and JAN TORE GRAN

ABSTRACT. ***Objective.*** To describe the prevalence and characteristics of non-inflammatory joint pain (NIJP) in patients with chronic inflammatory bowel disease (IBD) and its impact on patients' health related quality of life (HRQOL).

Methods. In a population based cohort, 521 patients (80%) were clinically investigated 6 years after onset of IBD. NIJP was defined as a history of joint pain during the last 3 months prior to examination and the absence of concomitant signs or symptoms of inflammatory or degenerative joint disease or chronic pain syndromes. HRQOL was registered by the generic Medical Outcome Study Short Form 36 (SF-36) and by the disease specific IBDQ.

Results. NIJP was reported by 85 (16%) patients and significantly more often in conjunction with Crohn's disease (CD, 22%) compared to ulcerative colitis (UC, 14%). The prevalence of NIJP was similar in men and women. No correlation with extension of intestinal disease, use of systemic medication, or frequency of surgery was found. NIJP exerted significant impact on HRQOL measured by SF-36 and IBDQ.

Conclusions. NIJP occurs frequently in IBD and more often in CD than in UC. NIJP significantly alters HRQOL and should be taken into account in trials estimating outcome in IBD and in clinical practice by attending clinicians. (J Rheumatol 2005;32:1755–9)

Key Indexing Terms:
ARTHRALGIA CROHN'S DISEASE INFLAMMATORY BOWEL DISEASE
JOINT PAIN QUALITY OF LIFE ULCERATIVE COLITIS

Patients with inflammatory bowel disease (IBD) frequently report joint pain. Hospital based studies indicate that a history of painful joints is reported by 30% of patients[1] and when clinically examined 7.8% complain of current joint pain[2]. However, estimates from population-based cohorts are not available, so prevalence of joint pain in a non-selected patient population with IBD remains unknown. In IBD, joint pain may be related to specific underlying disorders including IBD associated inflammatory rheumatic diseases or it may represent non-specific features[3]. Studies aimed at characterizing such non-inflammatory joint pain (NIJP) in IBD are, however, lacking.

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The possible impact of joint pain on clinical outcome and quality of life in IBD has not been fully investigated. The importance of measuring subjective aspects of patients' health, often referred to as health related quality of life (HRQOL), has become increasingly recognized in the last decade[4]. HRQOL questionnaires can be used to measure cross-sectional differences between patients or longitudinal changes over time. It is regarded necessary to use both a generic questionnaire, which generates a summary of health-related quality of life, as well as a disease specific questionnaire, which offers more detailed knowledge about the disease studied. Patients with chronic disorders often experience a burden of disease that may exert negative effect upon HRQOL. The occurrence of a concomitant disease in these patients can reinforce the already existing impairment of their HRQOL[5].

Our primary aim was to characterize NIJP and its frequency in a large population-based cohort of patients with IBD. Our secondary aim was to investigate possible impact of NIJP on HRQOL in patients with IBD.

MATERIALS AND METHODS

Study population. All newly diagnosed cases of IBD between January 1, 1990 and December 31, 1993 in 4 well-defined areas in south-eastern Norway (the counties of Oslo, Østfold, Telemark, and Aust-Agder) were recorded by the local departments of gastroenterology. To ensure complete ascertainment, all 1,236 general practitioners and clinicians at the 14 hos-

pitals of the 4 participating counties received information about symptoms consistent with IBD, and were invited to refer all potential cases of ulcerative colitis (UC) or Crohn's disease (CD) to the local gastroenterological outpatient clinic. A detailed presentation of the study design (The IBSEN-study) has been published[6,7].

In a systematic followup, all cases initially diagnosed with IBD and still alive were reviewed by gastroenterologists[8]. Patients were asked to participate in a structured interview and clinical examination by a rheumatologist (ØP). Of the 654 patients invited (454 with UC and 200 with CD), 521 patients (80%) responded to the invitation and underwent a clinical examination. There were 255 men and 266 women, with a mean age of 43 years (range 15-86 yrs).

Duration and extent of intestinal disease. The mean duration since onset of disease and since diagnosis were 85 and 73 months, respectively. In UC, proctitis was recorded in 100 cases (28%), left side colitis in 122 cases (35%), and extensive colitis in 131 cases (37%). In CD, 3 patients (2%) had upper gastrointestinal involvement, iliitis was recorded in 41 cases (24%), colitis in 62 cases (37%), and iliocolitis in 62 patients (37%). Information for the remaining 133 patients who did not attend the clinical investigation (33 patients had moved out of the area, 23 patients suffered from concomitant serious illness or were too old to participate, and 77 patients did not respond to the invitation) was based on hospital records, telephone interviews, mailed questionnaires, and case notes. Clinical characteristics and demographic data of these patients did not differ significantly from those investigated clinically[9].

Definition of rheumatic symptoms and diseases. By standardized interview, all patients were asked about pain in peripheral joints present during the last 3 months. A thorough clinical examination of painful joints was performed by an experienced rheumatologist (ØP). Radiological diagnostic investigations were performed only when considered necessary to confirm or rule out the presence of arthritis. Patients also underwent a standardized clinical investigation in order to identify well-defined inflammatory joint disorders or osteoarthritis meeting standard diagnostic criteria[10]. Pain was considered chronic and widespread if present for at least the last 3 months on both the left and right sides of the body and below and above the waist. Axial pain had to be present, following the American College of Rheumatology (ACR) 1990 criteria[11]. The diagnosis of fibromyalgia also followed 1990 ACR criteria requiring a history of chronic widespread pain and pain in 11 or more of 18 tender point sites on digital palpation[11]. NIJP was recorded when arthralgia of at least 3 months was present, without concomitant signs or symptoms of inflammatory or degenerative joint disease or chronic pain syndrome.

Assessment of health related quality of life. HRQOL was assessed using 2 different questionnaires. The Medical Outcome Study Short Form 36 (SF-36) is a generic questionnaire that assesses health concepts representing basic human values that are relevant to everyone's functional status and well-being[12]. The questionnaire is self-administered, consists of 36 questions, and assesses 8 dimensions of health including physical function, role limitations due to physical problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems, and mental health. The raw scores are transformed to a 0 to 100 scale, a higher score indicating better HRQOL. The SF-36 has been extensively validated in many countries and languages and in many patient groups. We used the Norwegian standard SF-36 version 1.0[13] to assess health status over the last 4 weeks.

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease specific QOL questionnaire[14]. It consists of 32 questions grouped into 4 underlying dimensions and a total score. The questionnaire has been translated into Norwegian (N-IBDQ) and a validation of the questionnaire has been published[15]. In contrast to the original IBDQ, the N-IBDQ consists of 5 dimensions: Bowel Function-I (Stool consistency and pattern, B1), Bowel Function-II (bowel pain and discomfort, B2), Social Function (SF), Emotional Function-I (E1), and Emotional Function-II (Worries, E2). The responses are graded on a 7-point Likert scale from 7 (not a problem) through 1 (a very severe problem), giving a possible total score range of 32 to 224. The higher the score the better the HRQOL.

All patients received the HRQOL questionnaires prior to rheumatological examination. They had the opportunity to complete them alone, without any disturbances, often in a separate room. The questionnaires were then checked for completeness, and if the patient had misunderstood or needed explanation to any question, such help was given.

Ethics. The study was approved by the Regional Ethics Committee and the Norwegian Data Registry. Confidentiality of both patient identity and records was maintained, using guidelines suggested by the National Health Department.

Statistics. Student's t test, Fisher's exact test, and chi-square test were used for statistical analyses and a p value of less than 0.05 was regarded as significant. Comparisons of QOL between UC and CD groups were performed using analysis of covariance (ANCOVA) estimating marginal mean scores with 95% confidence intervals adjusted for age and gender, as these covariates are known to influence HRQOL questionnaires.

RESULTS

Non-inflammatory joint pain. NIJP during the last 3 months was reported by 85 (16%) of the 521 clinically investigated patients (Table 1). Patients with CD were significantly more often affected by NIJP (22%) compared with UC (14%). However, the prevalence of NIJP was similar among men and women (Table 1), and the mean age of patients with NIJP was similar to those without NIJP.

Pain was monoarticular in 25 patients (4.8%), oligoarticular (2-5 joints) in 25 patients (4.8%), and polyarticular (> 5 joints) in 33 patients (6.3%). In 2 cases (0.4%), the number of involved joints could not be assessed. Knees were affected in 43 patients (8.3%), fingers or toes in 35 patients (6.7%), wrists in 19 patients (3.6%), hips in 17 patients (3.3%), ankles in 11 patients (2.1%), and shoulders in 10 patients (1.9%). Distribution of involved joints was similar between CD and UC and between men and women. Information regarding the onset of NIJP was not available in 3 cases (4%). Mean age at onset of NIJP was 37 years. Sixteen patients (19%) reported that occurrence of NIJP coincided with intestinal disease activity.

The extent of intestinal inflammation, use of systemic medication (prednisolone/prednisone, acetylsalicylic acid, sulfasalazine, azathioprine), and number of surgical interventions (intestinal resections in CD, colectomies in UC) did not differ between patients with and without NIJP. Mean

Table 1. Mean age at investigation and the prevalence of noninflammatory joint disease (NIJP) (n = 85) in patients with inflammatory bowel disease (IBD) comprising ulcerative colitis (UC) and Crohn's disease (CD).

	UC, n (%)	CD, n (%)	IBD, n (%)
Age, mean	46	39	43
Females	21 (12)*	23 (26)*	44 (17)
Males	27 (15)	14 (18)	41 (16)
Total	48 (14)**	37 (22)**	85 (16)

* Difference between females with UC and CD: p = 0.005. ** Difference between UC and CD: p = 0.009.

values of markers of systemic inflammation (erythrocyte sedimentation rate, C-reactive protein, and platelet count) were similar in patients with and without NIJP.

Health related quality of life. A total of 468 patients completed the 2 questionnaires. These patients did not differ from the non-responders with regard to mean age, gender, or medication. The estimation of SF-36 dimensional scores revealed that both UC and CD patients with NIJP had significantly lower scores in dimensions measuring bodily pain and social function compared to those without NIJP. Furthermore, in patients with UC and NIJP, scores reflecting general health, vitality, and mental health were lower compared to UC without NIJP. Finally, among patients with CD and NIJP scores of physical function and role emotion were significantly lower compared to those without NIJP (Table 2).

Evaluating the N-IBDQ, we found that among patients with UC, those reporting NIJP scored significantly lower (mean 173 points) than patients without NIJP (mean 189 points, $p < 0.001$). Similarly, patients with CD and NIJP had lower scores (mean 166 points) compared to those without NIJP (mean 184 points, $p = 0.002$). No difference between UC and CD was observed (Table 2).

DISCUSSION

NIJP was a quite common rheumatic complaint in this population-based cohort of patients, affecting 16% of our patients, studied 6 years after diagnosis of IBD. Based on the same cohort, we reported a point prevalence of IBD-related peripheral arthritis of 0.8%[9] and a prevalence of ankylosing spondylitis of 3.7%[16]. Furthermore, among these patients chronic widespread pain and fibromyalgia were found in 7.3% and 3.5%, respectively[17]. Thus, NIJP does seem to be the most common rheumatic complaint in patients with IBD. Unfortunately, due to variations in study design, it is difficult to compare our results with other studies, but some data may be extracted from previous hospital based publications. In a Belgian study, de Vlam and coworkers found a history of painful joints in as many as 30% of their patients[1]. In a British study by Orchard and coworkers, arthralgia was found in 7.8%[2]. Differing inclusion criteria and definition of NIJP prevent direct comparison of those studies with ours, but there is agreement that NIJP is a significant clinical problem. Estimates of NIJP in the general populations have shown a prevalence of 2-5%[18,19]. Consequently, NIJP seems to occur more frequently in patients with IBD than in the general population and our results indicate that NIJP may represent a major medical problem in IBD.

In the absence of clinical pathological findings such as inflammation, osteoarthritis or other joint disease, we found it unethical to systematically perform scintigraphy, magnetic resonance imaging (MRI), or invasive investigations. Consequently, we cannot completely rule out that a few cases of joint pain caused by subclinical inflammation or early osteoarthritis have been falsely included among patients with NIJP. We attempted to minimize the rate of misclassification with thorough clinical evaluation of each patient. However, in future studies the rate of possible subclinical inflammation may additionally be evaluated by more objective assessments, such as skeletal scintigraphy or MRI.

NIJP was more prevalent among patients with CD than in UC (22% versus 14%) (Table 1). This was also found by Orchard and coworkers, who observed arthralgia in 14.3% of their patients with CD compared to 5.3% in those with UC[2]. Moreover, de Vlam and coworkers found a history of painful joints among 35% of patients with CD compared with 16% in UC[1]. Thus all published series of patients with IBD report a higher incidence of NIJP in CD compared to UC. Explanations for the apparent discrepancy between CD and UC regarding occurrence of NIJP are lacking. In IBD, other clinical features, site of intestinal inflammation, intestinal complications, endoscopic, radiologic, and laboratory findings clearly indicate, however, that CD and UC repre-

Table 2. Health status in ulcerative colitis (UC) and Crohn's disease (CD) over the last 4 weeks measured by SF-36 scores in patients with and without non-inflammatory joint pain (NIJP). The questionnaire is self-administered, consists of 36 questions, and assesses 8 dimensions of health. The raw scores are transformed to a 0 to 100 scale. A higher score indicates better health related quality of life.

	NI Joint Pain		No Joint Pain	
	CD	UC	CD	UC
Health Dimension				
Physical function	76.18*	78.41	86.26	84.95
Role physical	55.88	62.50	69.33	70.58
Bodily pain	54.15*	56.30*	66.11	69.80
General health	51.97	54.20*	60.76	65.25
Vitality	44.85	47.50*	52.23	57.45
Social function	69.85*	73.86*	82.46	84.12
Role emotion	59.80*	70.45	75.63	74.91
Mental health	73.65	71.64*	77.21	79.16

* Significant difference between patients with and without NIJP ($p \leq 0.05$).

Table 3. The Norwegian Inflammatory Bowel Disease Questionnaire consists of 32 questions, grouped into 5 underlying dimensions and yielding a total score: Bowel Function-I (Stool consistency and pattern), Bowel Function-II (bowel pain and discomfort), Social Function, Emotional Function-I, and Emotional Function-II. The responses are graded on a 7-point Likert scale from 7 (not a problem) through 1 (a very severe problem), giving a possible total score range of 32 to 224. The higher the score, the better the health related quality of life.

	NI Joint Pain				No Joint Pain			
	CD		UC		CD		UC	
	F	M	F	M	F	M	F	M
Dimension								
Bowel function-I	39.87*	41.83	40.40**	41.89	43.51	42.22	43.86	44.34
Bowel function-II	21.00**	25.83	22.80	26.59	27.10	27.34	26.80	29.17
Social function	22.61*	24.33	25.07	24.78	25.35	25.22	25.17	26.47
Emotional function-I	48.35**	57.17	46.40**	55.52*	57.17	58.12	57.56	62.04
Emotional function-II	22.43*	25.67	22.73*	24.96	25.22	24.46	25.27	26.10
Total score	159.22**	179.58	162.33*	179.26*	184.46	183.10	184.42	194.23

* $p < 0.05$ NIJP vs no joint pain. ** $p < 0.001$ NIJP vs no joint pain.

sent 2 separate diseases[20]. Possible explanations for the difference in incidence of NIJP between CD and UC should be investigated with the aim of exploring the etiopathogenesis of NIJP.

In patients with NIJP we found a significantly lower HRQOL in the dimensions reflecting physical and mental functioning measured by SF-36 compared with patients without such joint pain (Table 2 and 3). Our data further indicate that NIJP has a clinically significant impact on patient HRQOL[21,22]. SF-36 has been included in many rheumatological studies, which makes it possible to compare HRQOL between patient groups. However such comparisons should be undertaken with caution because patients with chronic or serious disease may rate their quality of life higher compared to patients with acute or mild disease[23,24]. Nevertheless, data obtained from patients with rheumatoid arthritis[25], systemic lupus erythematosus[26], or Sjögren's syndrome[27] reveal more severe impact on HRQOL compared to our findings in patients with NIJP and IBD. Our data, obtained from the disease specific questionnaire IBDQ, seem to confirm those obtained by the SF-36. Although the impact of NIJP on the separate dimensions of HRQOL was not quite consistent, the total scores of IBDQ clearly showed a clinically significant reduction in score in patients with NIJP (Table 3). Consequently, our data indicate that NIJP has a clinically negative impact on patients' HRQOL measured by SF-36. Moreover, NIJP may negatively influence patients' disease specific HRQOL determined by IBDQ.

In summary, the prevalence and characteristics of NIJP that we found indicate that NIJP occurs frequently in IBD and more often in CD than UC. NIJP clearly alters the quality of life in patients with IBD and should not be neglected by the attending physician. The etiopathogenesis of NIJP in IBD should be further investigated and our findings should encourage others to undertake comparable surveys in controlled settings to extend our results and to further our knowledge of IBD.

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