# Arthropathies in inflammatory bowel disease : Characteristics and impact on daily functioning

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# CHAPTER 9

## Summary and general discussion

# SUMMARY

Inflammatory bowel disease (IBD) including Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC) is a chronic relapsing disease characterized by inflammation of the gastrointestinal tract.[1] Symptoms may be debilitating and include diarrhoea, abdominal pain and bloody stools. Besides abdominal symptoms, IBD is associated with different extra-intestinal manifestations (EIMs) including skin (e.g. pyoderma gangrenosum and erythema nodosum), ophthalmic (e.g. uveitis), liver (e.g. primary sclerosering cholangitis (PSC), cirrhosis, hepatitis) and rheumatologic (arthropathies) complications.[2] In the present thesis we mainly focus on the link between IBD and arthropathies. For decades, the pathophysiological overlap between arthropathies and IBD has been studied and the complex interplay between immunological, genetic, serological and therapeutic similarities have been highlighted.[3] Furthermore, in general, gastroenterologists are unfamiliar with the diagnosis and management of arthropathies. Therefore, a multidisciplinary approach together with rheumatologists by creating an efficient referral algorithm for the gastroenterologist that can be applied to IBD patients with arthropathies may be useful. Besides arthropathies, fatigue is a regular complaint in IBD patients.[4-5] Previous studies in patients with fatigue or systemic inflammation report brain changes and cognitive decline compared with healthy controls.[6-9] In this thesis we have presented results of a pilot study about this matter in quiescent IBD patients compared with healthy controls.



**Characteristics of arthropathies in IBD**

Arthropathies in IBD can be separated into inflammatory and non-inflammatory joint complaints and include both axial and peripheral joints.[10] Inflammatory joint complaints are a characteristic of spondyloarthritis (SpA), which covers different rheumatic disorders, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, juvenile SpA and IBD associated arthritis.[11] Non-inflammatory joint complaints, or arthralgia is the most common joint complaint in IBD.[10] In rheumatology, SpA can be classified according to rheumatologic classification criteria including the Amor, the European Spondyloarthropathy Study Group (ESSG), the Assessment of SpondyloArthritis international Society (ASAS) for both axial and peripheral SpA and the modified New York (mNY) criteria based on different SpA features.[12-14] In **chapter 3** we classified arthropathies in the IBD JOINT cohort according to these different criteria sets. Furthermore, we assessed which risk factors were associated with arthropathies in IBD and

we evaluated the disease course of arthropathies in IBD in the 1-year follow-up. The JOINT cohort included 255 IBD patients (155 with and 100 patients without self-reported arthropathies) who visited the JOINT outpatient clinic established by the department of rheumatology and the department of gastroenterology and hepatology of the Leiden University Medical Center (LUMC). At this outpatient clinic, all patients were seen at inclusion and after 1 year follow-up. During baseline visit and after 1 year follow-up, a routine medical history and data of EIMs was collected. In addition, a detailed rheumatologic examination was performed in all patients to assess the number of tender and/or swollen joints and radiographs of the pelvis, the lumbar and cervical spine and painful peripheral joints were conducted in patients with arthropathies. Only IBD patients who showed signs of inflammation during examination or on additional imaging were referred to the rheumatologist for further physical examination.[15]

In this chapter we concluded that the rheumatologic ASAS criteria for axial and peripheral joint complaints are the most applicable for IBD related inflammatory joint complaints. However, these criteria cannot be applied by gastroenterologists in daily practice to distinguish SpA from non-SpA, since these criteria are not intended for the use of diagnosis.[12-13] Orchard et al. proposed the Oxford criteria to classify IBD patients with peripheral arthropathies based on type 1 (oligoarticular) and type 2 (polyarticular) peripheral arthritis.[16] However, this classification system does not take axial arthropathies in IBD into account. Therefore, we proposed the Berlin algorithm for use by gastroenterologists to select IBD patients with chronic back pain with a high likelihood for axial SpA. This algorithm can be applied to discriminate patients with a high suspicion of axial SpA from the patients with low suspicion and may be used as a guidance to refer a patient to the rheumatologist. Patients with a proven sacroiliitis on the radiograph should be referred to the rheumatologist. In the patients without radiographic sacroiliitis, the presence of SpA characteristics is leading. SpA features include inflammatory back pain (IBP), enthesitis, dactylitis, uveitis, a positive family history for SpA, psoriasis, arthritis, a good response to NSAIDs and elevated Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). IBD patients with ≥ 3 SpA features have a high risk of having axial SpA, even without further information on human leukocyte antigen (HLA)-B27 testing or MRI of the sacroiliac joints. Patients with fewer SpA features should undergo HLA-B27 testing and especially if the HLA-B27 test turns out positive, referral for a rheumatologic examination should be considered.[17]

Besides axial SpA, a recommendation may be given to differentiate IBD patients with peripheral joint complaints with a high suspicion of peripheral SpA from patients with a low suspicion. At first, medical history, laboratory assessment and especially physical examination should differentiate if these musculoskeletal complaints are more prone to be inflammatory or not. Additionally, the presence of SpA features may be considered to decide if referral to a rheumatologist for rheumatologic examination and medical treatment is necessary.

In this chapter, we described that only 12.3% fulfilled the ASAS criteria for axial and peripheral SpA, with 9.7% (n=15) receiving a rheumatologic diagnosis of arthritis. This indicates that most of the IBD patients with arthropathies were classified with arthralgia (87.7%). Furthermore, we described in this longitudinal follow-up study that most of the patients with arthropathies reported peripheral joint complaints with more than one joint involved. The hand or the knee were the most frequently affected joints. Female gender, smoking and an active IBD disease were predictors of having arthropathies in IBD. During the 12-month follow-up, the proportion of IBD patients with arthropathies remained quite stable.

**The pathophysiological interplay between IBD and SpA**

Research on the pathophysiological link between IBD and SpA has been rapidly increasing over the past years. **Chapter 2** gives an overview of the most recently published studies on the clinical, genetic, immunological, serological, microbiotal and environmental overlap. TNF plays an important role in this interplay and is present in the lamina propria in IBD and in synovial tissue in SpA patients.[18] Subsequently, the use of TNF inhibitors has shown clinical and laboratory improvement in both inflammatory-mediated diseases.[19-20] In addition, the IL-23/Th-17 pathway plays an important role in the common immunology. IL-23 is found in the mucosa of the gut in IBD patients and in the synovial membrane of SpA patients. IL-23 plays a dual role in the gut with a protective and harmful activity. IL-23 activates Th-17 cells (including IL-17 and IL-22 cytokines) in which over-activation leads to an uncontrolled inflammatory status.[21] Furthermore a genetic link has been described concerning the presence of *HLA-B44* and *HLA-B27*, both located on chromosome 6, and the presence of CD and/or AS. Even an increased risk of the presence of HLA-B27 was seen in CD patients with an extended intestinal inflammation.[22-23] Increased serological biomarkers including anti-Saccharomyces cerevesiae (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-Eschericia coli outer membrane porin C

(anti-OmpC) and anti-flagellin (anti-CBir1) were found in IBD patients with ankylosing spondylitis (AS) compared with AS patients only. In addition, increased serum levels for anti-CBir1 and ANCA were found in AS patients compared with healthy controls indicating the presence of IBD serological biomarkers in AS patients.[24-25] Besides, fecal calprotectin (fCAL), a protein detected in the stool of IBD patients correlating the severity of the inflammation, was found in AS patients without subclinical signs of intestinal inflammation.[26] This chapter highlights also the environmental overlap between IBD and SpA. Dust exposure, cigarette smoking, vitamin D deficiency and stress seems factors associated both with IBD and SpA.[27-37] Based on these findings, we concluded that a pathophysiological overlap is present between IBD and SpA, but more research is necessary to examine this overlap more in depth since some contradictory results have been found in the literature.

In **chapter 4** we described the presence of rheumatoid arthritis (RA) biomarkers in IBD patients with and without arthropathies and in addition determined the frequency of biomarker positivity in these patients compared with RA patients. Levels of IgM rheumatoid factor (RF), IgA-RF, anti-cyclic citrullinated peptide 2 (anti-CCP2), anti-CCP3.1 and anti-carbamylated protein (anti-CarP) IgG and IgA were measured in the serum of IBD patients. These biomarkers were infrequently present in IBD patients with no differences in positivity between IBD patients with and without arthropathies. This implies that based on these results there is no need and clinical value to detect these RA markers in the serum of IBD patients with arthropathies.[38]



**Illness perceptions, coping strategies and outcomes in IBD**

Since previous studies described the impact of IBD on different illness outcomes including health related quality of life (QoL), work productivity and activity impairment,[39-41] we have highlighted in **chapter 5 to 7** of this thesis the effect of illness perceptions and coping strategies on these illness outcomes in IBD patients. Furthermore, we assessed the differences between these factors in IBD patients with and without arthropathies. Illness perceptions are the patients' ideas they create in order to understand their illness and to obtain control over the disease.[42] Coping strategies are cognitive and behavioural efforts to deal with the disease.[43] In **chapter 5** we have described in a cross-sectional study the mediating effect of coping strategies in the relationship between illness perceptions and outcomes in IBD patients via the Common Sense Model (CSM) by Leventhal et al.[44] Findings of this study indicate that more serious

consequences, a stronger personal control and less understanding of IBD were associated with more frequent use of the coping strategy 'decreasing activity' which was associated with a reduced mental and physical health and more activity impairment in IBD patients.[45] In this study, 'decreasing activity' seemed to be the only coping strategy mediating the effect of illness perceptions on outcomes. This is in concordance with earlier studies.[41,46-47] Besides the mediating effect of the coping strategy 'decreasing activity', patients with a lack of understanding of their IBD and patients who associate more negative emotions to their illness, reported less mental health. Subsequently, perceptions of severe consequences are associated with a reduced physical health and an increased activity impairment. In this cross-sectional study, having arthropathies was used as a covariate and was associated with a reduced physical health and more activity and work impairment.

In **chapter 7** we have demonstrated in a longitudinal study that IBD patients reported a reduced QoL and work productivity both at study inclusion and after 1 year follow-up.[3] Variables associated with a reduced QoL were having arthropathies, stronger beliefs about the consequences, the emotional impact of the disease and a lack of physical activity. Less work productivity was associated with the presence of arthropathies and negative ideas about the severity of the illness and the impact on daily functioning. Based on these results, we have concluded that IBD impacts the patients' ideas about the illness, their disease behaviour and daily functioning in different ways. Knowing this, the healthcare team may consider to focus on the patients' ideas and disease behaviour by modifying illness perceptions, coping strategies with the aim to improve illness outcomes by cognitive behavioural therapy (CBT). Previous studies in IBD patients have shown that CBT improved coping strategies and the QoL.[48-50] CBT comprises psychoeducation about the effect of the stress response and the association of this stress response and the presence of bowel complaints. In addition, this therapy may give insight into cognitive and behavioural responses to the IBD related symptoms and modify these responses to reduce distress related to the disease.[51] For patients who are not interested in CBT, behavioural or self-management therapy may be an effective alternative option. This type of therapy targets negative behaviours (including e.g. poor medication compliance) to improve overall physical and mental health.[52]



**Chapter 6** describes differences in illness perceptions, coping strategies and illness outcomes between IBD patients with and without arthropathies. This

chapter examined that stronger thoughts about the variability of symptoms, increased negative ideas about the effect and emotional impact of the illness on daily life and less understanding were illness perceptions more often perceived by the patients with arthropathies compared with patients without arthropathies. Additionally, patients with arthropathies were better in thinking of something nice and felt they were more useful to others. Furthermore, a reduced physical and mental health and more activity impairment was found in IBD patients with arthropathies compared with patients without arthropathies. The gastroenterologist needs to be informed about these differences in illness perceptions, coping and outcomes since these differences may impact the management process. However, no research has been performed on the effect of psychological therapy including CBT in IBD patients with arthropathies. Therefore, it is important that the maladaptive illness perceptions, coping strategies and outcomes in all IBD patients visiting the outpatient clinic will be addressed and might be changed by improving interventions via CBT or regular physical exercise.[48-53] Exercise programmes improve physical functioning and the general well-being and reduces stress in IBD patients. In the literature, it has been reported that stress may play a role in the development of IBD flares. Physical exercise decreases the level of stress in IBD and has a beneficial effect on the immune status and disease control.[53]



Additionally, we evaluated in this longitudinal study (**chapter 6**) the changes in illness perceptions, coping strategies and adjustment after 1 year follow-up in IBD patients with arthropathies compared with baseline scores. After 1 year follow-up, IBD patients with arthropathies were less convinced about the efficacy of medical treatment compared with baseline. This may be due to the fact that still most of the patients experienced arthropathies after 1 year. In addition, these patients reported an active IBD based on the Harvey Bradshaw Index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI) above 4. In chapter 3, we found an association between IBD disease activity measured with the HBI and the presence of arthropathies, indicating that these patients with an HBI > 4 were more prone for having arthropathies.[15] This implies the importance of targeting IBD remission via medical interventions, and besides, to take into account the illness perception 'treatment control' by trying to give advice about the need of medical treatment to reduce complaints. Furthermore, the IBD patients with arthropathies were better able to adjust their daily activities to their complaints at follow-up compared with scores at baseline. This demonstrates that after some time, IBD patients with arthropathies will get used to

their illness. This is in contrast with RA and DM patients who perceived less effort to reduce and were less able getting used to the symptoms related to their illness.[54]

**The gut-brain axis?**

Besides arthropathies, more EIMs have been associated with IBD. Since previous studies report the association with systemic inflammation and brain changes[6-9], we assessed in this thesis brain involvement in quiescent CD patients with fatigue by making use of different Magnetic Resonance Imaging (MRI) techniques and neuropsychological examination. In **chapter 8** we found neurochemical, perfusion and mental brain changes in quiescent CD patients with fatigue compared with healthy controls.[55] No differences were found in subcortical volume structures. A reduced glutamate + glutamine concentration and ratio to total creatine were found in CD patients compared with healthy controls. Glutamate receptors are present in the hippocampus and the neurotransmitter is associated with mood and memory.[56] Glutamine is involved in the energy metabolism of the brain.[57] Furthermore, increased cerebral blood flow (CBF) was found in CD patients compared with controls probably due to a compensatory mechanism in response to the inflammation causing eventually injury.[58-60] More depressive symptoms and an association between depression and reduced cognitive scores, including executive functioning and memory, was seen in CD patients compared with healthy controls. Previous studies demonstrated a link between reduced brain volumes due to inflammation and cognitive deficits.[61-62] This association has not been seen in our study, since no reduced brain volumes were detected in CD patients compared with controls. Based on the results outlined in this chapter, we advise the clinician to pay attention to the effect of systemic inflammation, despite the HBI score < 4 indicating a quiescent disease, and the effect of fatigue complaints on brain changes in CD patients. Cognitive functioning and mood is important in daily life and based on results presented in **chapter 8,** a gastroenterologist should be aware of a deficit in this cognitive and mood domain in CD patients.

# FUTURE PERSPECTIVES

How should a gastroenterologist manage an IBD patient with arthropathies at their outpatient clinic? This thesis highlights IBD patients with arthropathies from different points of view and results presented in this thesis should be the start of creating more awareness about this matter. At first, it is important for the gastroenterologist to distinguish inflammatory joint complaints (including axial and peripheral SpA) from arthralgia in order to be able to provide the best management for the IBD patient. Moreover, this may help in reducing the number of IBD patients with musculoskeletal complaints that need to be referred to the rheumatologist. Since the rheumatologists have more knowledge about the management of inflammatory joint complaints compared with gastroenterologists, the IBD patients with peripheral and/or axial SpA are best treated by rheumatologists. IBD patients with arthralgia may remain under supervision of the gastroenterologist since rheumatologists do not have additional medical interventions to treat arthralgia.

The distinction between inflammatory joint complaints and arthralgia should be made by physical examination and patient history taking the different SpA features as described in **chapter 3** into account. The Berlin algorithm may be used in patients with the suspicion of axial SpA. Positive SpA features, together with a rheumatologic examination of swollen peripheral joints will make IBD patients more suspect for having peripheral SpA.[17] Future studies could investigate the importance of the role of SpA features and the Berlin algorithm in IBD patients with arthropathies to discriminate patients more suspect for axial and/or peripheral SpA from patients with arthralgia. In total, approximately 30% of the IBD patients have musculoskeletal complaints.[63] However, as mentioned in **chapter 3**, most of the IBD patients with self-reported arthropathies were classified with arthralgia and remain under supervision of the gastroenterologist. This matter in combination with the impact of having IBD-associated arthropathies on illness perceptions, coping strategies and illness outcomes highlighted in **chapter 5 to 7** emphasize the need for a recommendation about how these IBD patients with arthropathies could be approached and treated at the outpatient clinic. A first step in the development of this recommendation can be made by designing a training program about the characteristics, risk factors, diagnostics and interventions that should be made in IBD patients with arthropathies. This training program may be created together with rheumatologists and could be offered to all gastroenterologists in training as a part of their requirements.

This training should at first highlight the differences between inflammatory and non-inflammatory joint complaints by applying the SpA features and Berlin criteria for axial SpA. Second, the association between having arthropathies in IBD and a female gender, smoking and an active IBD disease could be mentioned. Third, the different illness perceptions and coping strategies perceived by both IBD patients with and without arthropathies, the impact on daily functioning and possible (psychological) interventions including CBT may be included. Informing gastroenterologists creates awareness for arthropathies in IBD. Still numerous IBD patients are not aware of the association of IBD and arthropathies and do not mention their joint complaints at the IBD outpatient clinic. Therefore, the gastroenterologist should consider to ask IBD patients regularly about symptoms of joint complaints at the outpatient clinic.

In **chapter 3** we have described that female gender (Odds Ratio (OR) 1.97, p=0.02), smoking (OR 2.28, p=0.03) and an active IBD disease (OR 4.07, p<0.001) were predictors of having arthropathies in IBD. Since active IBD disease is a predictor of arthropathies, the gastroenterologist could consider to aim for IBD disease remission by applying the 'treat to target' strategy. This strategy could result in IBD remission and may contribute to a reduction of IBD associated joint complaints.[64-65] Subsequently, the gastroenterologist may consider to inform patients about the importance of stop smoking. Severs et al. describe that smoking cessation in IBD patients resulted in a rapid decrease of joint complaints compared to levels encountered in patients who had never smoked.[66]



For IBD patients with arthralgia, it is important to reduce pain by applying different interventions. At first, analgesics should be considered including paracetamol, COX-2 inhibitors or eventually opioids to reduce the symptoms of arthralgia.[67] Besides symptom control by drug therapy, there is growing evidence that self-management and physical activity is important in the management of arthralgia. Research has been performed in patients with musculoskeletal complaints and confirmed that performing long-term exercise has a positive effect on the functional ability by reducing the pain and improving muscle strength and the general well-being by increasing personal confidence and ultimately reducing unemployment. The most important aspects of improving physical activity is the patients motivation and knowledge about the reason of improving physical activity.[68] It is the job of a health professional to place sufficient emphasis on promoting this physical activity and explaining the effect of physical activity on the patients' complaints.

Furthermore, since illness perceptions and coping impact illness outcomes including QoL and work and activity impairment in IBD patients with and without arthropathies, psychological interventions may be considered in this patient population as well. These interventions should reduce negative thoughts and underlying beliefs created and may change behavioural patterns related with the disease. Different studies in patients with diverse health problems or disorders, including IBD patients, show positive results of CBT on health outcomes, coping and pain control compared with the control group. These interventions are a promising health care development since interventions can be easily offered via the internet (e-health therapy), which reduces travelling time, gives the patient more autonomy to decide when to participate, reduces waiting lists and may save therapists time.[69-72] Unfortunately, no research has been performed on the effect psychological interventions and e-health therapy on illness perceptions, coping and outcomes in IBD patients with arthropathies and may be considered to be conducted in the future.

Based on previous mentioned interventions, the development of management recommendations for IBD patients with arthropathies for the gastroenterologist should be considered. To substantiate the evidence for these recommendations additional longitudinal prospective follow-up studies may be considered to compare different interventions applicable in daily clinic (e.g. drug therapy, e-health therapy, CBT and physical exercise) in IBD patients with arthropathies to reduce joint complaints and their effect on daily functioning. Additionally, it may be considered to pay more attention to illness perceptions, coping strategies, QoL and activity impairment during consultation at the outpatient IBD clinic by involving a specialized psychologist. Marin-Jimenez et al. reported that less than 25% of the IBD patients with psychological problems leading to a decreased QoL were referred to psychiatry or psychological services. However, approximately 80% of the total IBD population found it necessary that physicians paid attention to the impact of IBD on the psychological state during regular visits. Furthermore, they agreed that a clinical psychologist should be part of the healthcare team.[73] Based on these findings it is suggested that a psychologist specialized in chronic diseases could be involved in the management of patients with IBD.

As described in **chapter 4** and based on previous research presented in **chapter 2** there is no additional value to detect RA serological biomarkers in IBD patients with arthropathies in clinic, which confirmed the data of Papamichael

et al., and demonstrated that the pathogenesis of arthropathies in IBD is not mediated by anti-CCP antibodies.[74] Anti-CCP has been previously reported to be a prognostic marker for the development of RA.[75-76] This difference in serological biomarkers indicates that RA and arthropathies in IBD are different musculoskeletal diseases with a contrasting pathophysiology and should be managed in a different way.

Besides having arthropathies, many IBD patients report chronic fatigue. Chronic fatigue is associated with an active IBD disease and impaired health-related QoL.[4-5] However, still 40% of the quiescent IBD patients report chronic fatigue as well. In **chapter 8** we gave an overview of the systemic effects of quiescent CD on the brain assessed by different MRI techniques and neuropsychological examination in patients with fatigue. Since this is to our knowledge the first pilot study in which this systemic effect on the brain has been evaluated, more studies are needed to confirm our findings. Understanding more precisely the pathophysiology of brain changes due to systemic inflammation and fatigue in IBD may lead to new therapeutic targets in the management of this inflammatory disease.

# GENERAL CONCLUSION



This thesis aimed to provide an insight in arthropathies in IBD highlighted from different points of view: the common pathophysiology between IBD and SpA, the clinical characteristics associated with arthropathies in IBD and illness perceptions, coping strategies and outcomes related to it. A recommendation may be considered for gastroenterologists about the recognition and management of the different joint complaints in IBD patients with arthropathies. At first, medical history and additional (rheumatologic) examination checking evident joint swelling should be performed. This should include the assessment of the presence of the different SpA features, which if present, increase the suspicion for having axial and/or peripheral SpA. Subsequently, laboratory assessment including HLA-B27 testing and additional imaging may be performed, however, this is frequently mainly indicated after a rheumatologic consultation. In case of a low likelihood of SpA, expensive referral to the rheumatologist may be avoided and may prevent a time-consuming process for the patient. By creating more awareness about the different types of arthropathies associated with IBD and informing gastroenterologists about differentiating IBD patients with inflamma-

tory arthropathies by focusing on SpA features for axial and peripheral SpA, we think the first step has been made in the management of these patients. Furthermore, in the future, a multidisciplinary outpatient clinic including a gastroenterologist, a rheumatologist and a psychologist may be considered to optimise the care for IBD patients both with and without arthropathies.

In conclusion, arthropathies in IBD is the most common EIM and may affect the IBD patient in different ways. More awareness should be created and ideally, attention for joint complaints should become part and parcel of daily management of patients with IBD.

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