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

Erp, S.J.H. van

ARTHROPATHIES IN INFLAMMATORY BOWEL DISEASE

Characteristics and impact on daily functioning

Sanne J.H. van Erp

Arthropathies in inflammatory bowel disease
Characteristics and impact on daily functioning

ISBN: 978-90-9030778-7
Cover design and layout: evelienjagtman.com
Printing: Printforce, Alphen a/d Rijn, the Netherlands

ARTHROPATHIES IN INFLAMMATORY BOWEL DISEASE

Characteristics and impact on daily functioning

PROEFSCHRIFT

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus Prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 13 februari 2018
klokke 16.15 uur

Door Sanne J.H. van Erp
geboren te Made, 1991

Promotores

Prof. dr. D.W. Hommes, Center for Inflammatory Bowel Diseases,
University of California Los Angeles, Los Angeles, USA
Prof. dr. D. van der Heijde

Co-promotor

Dr. A.E. van der Meulen-de Jong

Leden promotiecommissie

Prof. dr. ir. H.W. Verspaget
Prof. dr. J.C.H. Hardwick
Prof. dr. M. Kloppenburg
Dr. F.A. van Gaalen
Dr. H.H. Fidder, Universitair Medisch Centrum Utrecht, Utrecht
Prof. dr. G. Dijkstra, Universitair Medisch Centrum Groningen, Groningen

TABLE OF CONTENTS

CHAPTER 1

General introduction and outline of the thesis

Inflammatory bowel disease (IBD) covers Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC).[1-4] IBD is a chronic disease, with a multifactorial cause including autoimmune, genetic and environmental factors, in which antibodies are created that affect the intestinal wall leading to chronic inflammation.[1-2] The diagnosis of IBD is based on medical history, complaints of the patient, physical examination and endoscopy and/or additional imaging. The suspicion for IBD will increase with the presence of blood in the stool, weight loss, a positive family history and clinical signs of inflammation including fever and diarrhoea. It is important to bear in mind that age is also an important factor for the diagnosis of IBD. Blood loss at a young age (below 50 years) is more suspect for haemorrhoids, while blood loss at an old age (above the age of 50 years) is more likely to be caused by an adenoma or carcinoma. IBD occurs at any age, but with a peak onset in young adults between the age of 15-35 years with an incidence rate of 1 per 1000 individuals.[3] The kind of intestinal symptoms a patient presents at the outpatient clinic depends mainly on the location of the IBD. UC is the most prevalent type of IBD in which only (a part of) the colon is affected. In CD, the whole GI tract can be involved.[1-2] IC concerns approximately 10% of the IBD patients and comprises the ones in whom the diagnosis of CD or UC cannot be made based on clinical testing including colonoscopy, biopsy and laboratory tests.[4]

Besides gastrointestinal symptoms due to intestinal inflammation, IBD may manifest outside the intestine, the so-called extra-intestinal manifestations (EIMs). Arthropathies in IBD are the most common EIM with a prevalence of 30%. Other EIMs that may be present in IBD patients involve the skin, eyes or liver.[5] IBD is characterized by periods of disease flares and remission.[1-4] The treatment depends on the diagnosis of CD or UC and whether the disease is active or not. The treatment of IBD is intended to induce and maintain IBD remission and prevent disease progression by applying long-term medical therapy.[1-2] New trends in the IBD management is the 'tight control monitoring' and the 'treat to target' strategy which focusses on frequently assessment of disease activity by markers of inflammation with the ideal target to achieve mucosal healing, meaning the absence of inflammatory and ulcerative lesions in the intestine.[6] However, this management seems not applicable to arthropathies in IBD, since not only disease activity is a predictor of the development of arthropathies in IBD. Furthermore, different kinds of arthropathies may be present in IBD patients, subdivided into inflammatory and non-inflammatory joint complaints. These inflammatory and non-inflammatory joint complaints

may have different treatment options.[7] A new management approach for these patients may be considered to be developed for gastroenterologists, taking the characteristics and treatment options of arthropathies in IBD into account.

Outline and aims of the studies described in this thesis

Since arthropathies are the most common EIM in IBD we aimed to highlight this matter in the present thesis in different ways to create more awareness among gastroenterologists about the characteristics and the burden of arthropathies on daily functioning in IBD. This thesis will provide an overview of the different types of arthropathies in IBD and the risk factors associated with it. Additionally, this thesis proposes an efficient referral algorithm for the gastroenterologist to discriminate the IBD patients with a high suspicion of inflammatory joint complaints from the patients with a low suspicion. Furthermore, the impact of having IBD only and the impact of having IBD including arthropathies on illness perceptions, coping strategies and daily functioning will be emphasized.

Arthropathies in IBD can be subdivided into inflammatory (typically a characteristic of Spondyloarthritis, SpA) and non-inflammatory joint complaints, also known as arthralgia.[8] Previous performed studies showed a pathophysiological overlap between IBD and SpA.[9] An overview of this overlap is described in **chapter 2**. This scoping review provides an insight in the common immunological, genetic, serological, microbiotical and environmental factors in both chronic diseases.

The chapters 3 till 7 of this thesis are based on the JOINT cohort. All patients who visited the outpatient clinic of the Leiden University Medical Center (LUMC), the Netherlands, from July 2009 to February 2010 were asked to complete a questionnaire to assess whether they reported joint complaints. IBD patients with and without self-reported arthropathies were invited to attend the JOINT outpatient clinic, which was initiated by the department of Gastroenterology and Hepatology and the department of Rheumatology of the LUMC. Inclusion was limited to 255 patients (155 IBD patients with, 100 patients without arthropathies) to guarantee optimal care for the participants. All patients were seen at study inclusion and after 1 year follow-up at the JOINT clinic. At both time points, routine medical history and data of EIMs was collected. Furthermore, rheumatologic examination, laboratory assessment (including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and (human leukocyte antigen) HLA-B27) and radiographs of the affected joints was performed in patients with arthropathies. Only the IBD patients who showed signs of inflammation during

rheumatologic examination at the outpatient clinic or on the radiographs were referred to the rheumatologist for further examination. All participants were requested to complete monthly questionnaires to assess IBD disease activity and spine and/or peripheral joint scores. Additional questionnaires were completed at baseline and after 12 months follow-up to assess illness perceptions, coping strategies and illness outcomes including the quality of life (QoL), work and activity impairment.

In **chapter 3,** we characterised the different joint complaints in the JOINT cohort using validated rheumatologic classification criteria. Furthermore, risk factors associated with having arthropathies in IBD were described.

In rheumatoid arthritis (RA), different biomarkers have been reported to be important diagnostic markers and predictive for the development of RA at an early stage.[10-16] However, although arthropathies are common in IBD, there is a lack of biomarkers in clinical practice predictive for the development and onset of arthropathies in IBD. **Chapter 4** evaluates the presence of rheumatologic biomarkers in the serum of IBD patients with arthropathies and compares biomarker positivity with the serum of RA patients. If present, biomarkers may help in diagnosing arthropathies in IBD at an early stage.

From the literature, it is well known that IBD has an impact on illness perceptions, coping and outcomes including quality of life (QoL).[17-19] Illness perceptions are personal beliefs and cognitions about the disease. Coping strategies are personal efforts created to deal with the IBD. In this thesis, different illness outcomes have been examined including QoL, subdivided into mental and physical health, work and activity impairment. We assessed in **chapter 5 to 7** the different illness perceptions, coping strategies and illness outcomes in IBD patients with and without arthropathies. **Chapter 5** describes the mediating effect of coping on the association between illness perceptions and outcomes by making use of the Common Sense Model (CSM) in IBD patients. **Chapter 6** illustrates the association between having arthropathies in IBD and illness perceptions, coping and outcomes compared with patients without arthropathies. The effect of arthropathies, illness perceptions and coping strategies on the QoL and work productivity has been evaluated in **chapter 7**.

Besides having arthropathies, IBD patients may suffer from mood disorders, fatigue or cognitive decline. In the literature, studies describe the correlation

of systemic inflammation and mood disorders and/or cognitive decline.[20-22] A pilot study in which brain involvement is evaluated in quiescent CD patients with fatigue by Magnetic Resonance Imaging (MRI) and neuropsychological examination and compared with healthy controls without fatigue is presented in **chapter 8.**

Chapter 9 outlines the most important findings of the different studies presented in this thesis and results are discussed in future perspectives. A summary of this thesis in Dutch is presented in **chapter 10.**

REFERENCES

1. Torres J, Mehandru S, Colombel J, et al. Crohn's disease. Lancet 2017;389:1741–55.
2. Torres J, Mehandru S, Colombel J, et al. Ulcerative colitis. Lancet 2017;389:1756–70.
3. Zhang Y, Li Y. Inflammatory bowel disease: Pathogenesis. World J Gastroenterol 2014;20(1):91-99.
4. Tremaine WJ. Diagnosis and Treatment of Indeterminate Colitis. Gastroenterol Hepatol 2011;7(12):826–28.
5. Card TR, Langan SM, Chu TP. Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported. Dig Dis Sci 2016;61(9):2619-26.
6. Palmela C, Torres J, Cravo M, et al. New Trends in Inflammatory Bowel Disease. GE Port J Gastroenterol 2015;22(3):103-11.
7. Van Erp SJ, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2016;10(2):166-75.
8. 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.
9. De Wilde K, Debusschere K, Beeckman S, et al. Integrating the pathogenesis of spondyloarthritis: gut and joint united? Curr Opin Rheumatol 2015;27(2):189-96.
10. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: clinical applications. Dis Markers 2013;35(6):727-34.
11. Kudo-Tanaka E, Ohshima S, Ishii M, et al. Autoantibodies to cyclic citrullinated peptide 2 (CCP2) are superior to other potential diagnostic biomarkers for predicting rheumatoid arthritis in early undifferentiated arthritis. Clin Rheumatol 2007;26:1627-33.
12. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis 2010;69:490-94.
13. Dos Anjos LM, Pereira IA, d'Orsi E, et al. A comparative study of IgG second- and third generation anti-cyclic citrullinated peptide (CCP) ELISAs and their combination with IgA third-generation CCP ELISA for the diagnosis of rheumatoid arthritis. Clin Rheumatol 2009;28(2):153-58.
14. Shi J, Knevel R, Suwannalai P, et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc Natl Acad of Sci U S A 2011;108:17372–77.
15. Shi J, van Veelen PA, Mahler M, et al. Carbamylation and antibodies against carbamylated proteins in autoimmunity and other pathologies. Autoimmun Rev 2014;13(3):225-30.
16. Verheul MK, van Erp SJ, van der Woude D, et al. Anti-carbamylated protein antibodies: a specific hallmark for rheumatoid arthritis. Comparison to conditions known for enhanced carbamylation; renal failure, smoking and chronic inflammation. Ann Rheum Dis 2016;75(8):1575-76.
17. Casati J, Toner BB. Psychosocial aspects of inflammatory bowel disease. Biomed Pharmacother 2000;54:388-93.
18. Casati J, Toner BB, de Rooy EC, et al. Concerns of patients with inflammatory bowel disease. Dig Dis Sci 2000;45:26-31.

19. Bernklev T, Jahnsen J, Henriksen M, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12:402-12.
20. Wang PI, Cagnoli PC, McCune WJ, et al. Perfusion-weighted MR imaging in cerebral lupus erythematosus. Acad Radiol 2012;19:965-70.
21. Zonis S, Pechnick RN, Ljubimov VA, et al. Chronic intestinal inflammation alters hippocampal neurogenesis. J Neuroinflammation 2015;12;65.
22. Zimmermann N, Corrêa DG, Kubo TA, et al. Global cognitive impairment in systemic lupus erythematosus patients: A structural MRI study. Clin Neuroradiol 2017;27(1):23-29.

CHAPTER 2

Common pathophysiology between inflammatory bowel disease and spondyloarthritis: a review

S.J.H. van Erp, F.A. van Gaalen, D.W. Hommes, D. van der Heijde,
A.E. van der Meulen-de Jong

ABSTRACT

In inflammatory bowel disease (IBD), arthropathies are the most common extra-intestinal manifestation (EIM) and associated with female gender, smoking and IBD disease activity. Arthropathies in IBD can be subdivided into spondyloarthritis (SpA), a form of inflammatory joint complaints, or arthralgia, non-inflammatory joint complaints. The understanding of the pathophysiological overlap between IBD and SpA and as a result the interest of a multidisciplinary approach to IBD patients with arthropathies has increased in the past years. In this narrative review, the common immunological, genetic, microbiotical, serological and environmental factors of IBD and SpA will be discussed.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammation of the intestine and can be subdivided into Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). CD causes transmural inflammation and may affect the entire gastrointestinal tract. UC is characterized by mucosal inflammation and is generally limited to the colon.[1-2] IC comprises approximately 10% of the IBD patients and concerns the ones in whom the diagnosis of CD or UC cannot be made based on clinical testing including colonoscopy, biopsy and laboratory assesment.[2] The aetiology of IBD is an interplay of different factors including immune response, genetic susceptibility, the intestinal microbiome and the external environment. The incidence of CD in the western world is approximately 10.6 per 100000 persons and the incidence of UC is approximately 24.3 per 100000 individuals.[3-4] These numbers are increasing for example due to industrialization causing changes to microbial exposures, diet, lifestyle behaviours, medication and pollution exposures, all suspected as potential environmental risk factors for IBD.[5-6]

IBD is associated with a variety of extra-intestinal manifestations (EIMs) of which arthropathies are the most common with a prevalence of 30%.[7] Female gender, smoking or an active IBD disease are factors contributing to the development of arthropathies in IBD.[8] IBD-associated arthropathies can be subdivided into spondyloarthritis (SpA; inflammatory joint complaints) and arthralgia (non-inflammatory joint complaints). SpA is a group of rheumatic disorders, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, juvenile SpA, IBD related arthritis and undifferentiated SpA (uSpA), of which AS is the most characteristic.[9] In Europe, a SpA prevalence rate of 0.54 (95%CI 0.36-0.78) has been described.[10] In general, SpA includes both axial and peripheral arthritis and this is similar in IBD patients with SpA. Axial arthritis results in back pain, while peripheral arthritis affects most frequently the hand and knee joints.[9] It is important to differentiate IBD-associated axial and peripheral SpA from arthralgia in a diagnostic work up. Patients with a diagnosis of SpA can be classified using the Assessment of SpondyloArthritis international Society (ASAS) criteria.[9,11-12] Two separate ASAS classification sets exist: one for axial SpA and one for peripheral SpA covering different SpA features. SpA features used in the criteria include uveitis, IBD, psoriasis, dactylitis, enthesitis, arthritis, inflammatory back pain (IBP), a good response to NSAIDs, elevated acute phase reactants, the presence of human leukocyte antigen (HLA)-B27 or a positive

family history for SpA in addition to imaging of the sacroiliac joints.[11-12] Most of the IBD patients with arthropathies do not fulfil the ASAS criteria and will be diagnosed with arthralgia. Nevertheless, according to previous research, approximately 12% of the IBD patients with arthropathies can be classified with axial and peripheral SpA based on the ASAS criteria.[8]

In the literature, studies indicate a genetic and symptomatic link between SpA and IBD.[13] From studies performed with SpA patients without bowel symptoms, we know that asymptomatic bowel inflammation may be present. On the long-term, disappearance of joint inflammation was associated with IBD remission and vice versa. Moreover, SpA patients were more prone for developing IBD in the future.[14-16]

Understanding precisely the pathophysiology between SpA and IBD, may improve treatment of arthropathies in IBD. This review clarifies the overlap in pathophysiology between IBD and SpA by highlighting this from an immunologic, genetic, microbiotical, serological and environmental point of view. A scoping literature search was performed until December 2016.

IMMUNOLOGY

Tumor necrosis factor (TNF)

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine which regulates varied aspects of the immune response in autoimmune diseases via the interaction with the TNFR1 and TNFR2 receptor. TNFR1 mediates especially the pro-inflammatory and cell death pathways, known as apoptosis, by activation of the adaptor proteins TNFR1-associated death domain (TRADD) and Fas-associated death domain (FADD). TNFR2 promotes tissue repair and angiogenesis via the pro-survival transcription factor nuclear factor-kB (NFkB) and T-cell receptor activation via TNFR2 expression on T-regulatory (Treg) cells.[17-18] TNF is produced by different cells including monocytes, macrophages, T and B lymphocytes, natural killer (NK) cells, neutrophils and endothelial cells. TNF is important for the host defence to infection, but excessive production may be harmful.[19] Many of the pro-inflammatory effects are based on vascular endothelium and leukocyte interactions. As a response to TNF, cytokines and chemokines (including interleukin (IL)-8, IL-1, IL-6, IFN-gamma-inducible protein (IP)-10 and Monocyte Chemoattractant Protein (MCP)-1) induce inflammation by leukocyte adhesion.

Local effects of TNF are vasodilatation, increased blood flow and increased trans-endothelial migration of macromolecules and vascular leak causing oedema.[20-21]

In IBD, TNF reactivity is increased in the lamina propria. In SpA, TNF is increased in the inflamed joint caused by activated synovial macrophages leading to inflammation of synovial tissue. Kontoyiannis et al. examined that when TNF was overexpressed in mice with arthritis, IBD developed probably through migration of macrophages and lymphocytes from the joint to the gut.[22] Westlund et al. found a common aetiology of chronic arthritis and gastrointestinal infections through environmental factors and genetic deficiency of the TNFR1/R2 receptors causing chronic elevations of TNF levels in the serum.[23]

The introduction of the TNF inhibitors has shown a clinical and laboratory improvement in both SpA and IBD compared with placebo treatment.[24-26] TNF inhibitors reduce cytokine production and vascular activation causing inflammation. Anti-TNF drugs induce and maintain remission and relapse of the disease after discontinuation is common in both SpA and IBD.[27-28]

The IL-23/IL-17 axis

Different cytokines play a role in the common pathophysiology of IBD and SpA, also known as the joint-gut axis. Recently it has been proposed that the IL-23/IL-17 cytokine axis contributes to the pathogenesis of both IBD and SpA, and comprises the IL-23, IL-21, IL-22 and IL-17 cytokines.[29] IL-23 is a key factor and stimulates (T-helper) Th-17 cells, differentiated from naïve CD4+ T-cells, to produce a prolonged up-regulation of different cytokines including IL-17, IL-22, TNF, IL-1β and IL-6. IL-23 is found in the intestinal mucosa of patients with IBD, in the synovial membrane of RA patients and in the skin of patients with psoriasis.[30] In the intestine, IL-23 plays a binary role with both protective and harmful functions. Disruption of immune homeostasis through inflammatory effects up-regulates IL-23 synthesis leading to over-activation of the immune response and eventually chronic mucosal inflammation.[31]

IL-17 induces production of cytokines and chemokines (e.g. IL-6 and IL-8, IL-1β, IL-21, TNF-α, IFN-γ) and attracts neutrophils to different inflammation sites. Gheita et al. reported that the concentration of the IL-23 cytokine in the serum was significantly higher in the IBD patients with arthritis or sacroiilitis compared with IBD patients without joint complaints. In addition, IL-23 cytokine levels were

higher in CD patients compared with UC patients.[30] However, Dmowska-Chalaba et al. did not find a difference in IL-23 cytokine concentration between patients with IBD-related SpA or IBD only, probably due to a relatively small cohort size and the fact that IBD activity had not been taken into account.[32] Ciccia et al. examined the expression of the IL-23/IL-17 pathway in patients with CD and AS. IL-23 was up-regulated in AS patients to concentrations comparable with concentrations in CD patients, in which the Paneth cells of the terminal ileum were the origin of IL-23 producing cells. IL-23 was never detected in healthy controls. CD patients presented an increase in IL-17, IL-6 and IL-1β expression in the serum, supporting the presence of the IL-23/IL-17 pathway in CD.[33] Involvement of the Th-17 pathway in SpA patients was supported by Singh et al. who concluded that levels of IL-17, IL-6, TGF-β and IFN-γ were increased in the sera and synovial fluid of SpA patients and increased numbers of Th-17 cells had been found in the peripheral blood.[34]

Targeting IL-23 or IL-17 receptors seems to be effective and a potential approach in the treatment of chronic inflammatory diseases including SpA and IBD.[35-37]

GENETICS

Besides immunology, there is an increasing interest in the common genetic background of SpA and IBD. In recent years, we have witnessed rapid advances in the understanding of the genetic basis of IBD. Family history is a risk factor for developing IBD, indicating a genetic influence in this disease. Genetic loci involved in IBD display different pathways that are essential for microbial defence, autophagy and the regulation of adaptive immunity all leading to intestinal homeostasis. Different genes and alleles may be protective or predisposing. More than 50% of the IBD susceptibility genes have been associated with other inflammatory (autoimmune) diseases. These overlapping genes may have similar or contrasting effects in the different diseases.[38] Similarly, studies of familial aggregation and disease concordance in twins with SpA indicate the contribution of genetic factors in the presence of SpA for approximately 90%.[39] Bjarnason et al. described that first-degree relatives of AS patients were more prone to develop subclinical gut inflammation and suggested this was due to the genetic overlap between both diseases. Vice versa they found sacroiliitis in patients with subclinical intestinal inflammation on computerized tomographic (CT)-scan.[40]

Recent literature reports that over 200 genetic regions are associated with IBD. Among these, multiple are involved in the IL-23/Th-17 network (including *IL23R*, janus kinase 2 (*JAK2*), tyrosine kinase 2 (*TYK2*) and signal transducer and activator of transcription (*STAT)3*). Other noteworthy susceptibility genes in IBD are the nucleotide-binding oligomerization domain-containing gene *(NOD)2*, the caspase recruitment domain-containing gene *(CARD)9* and the autophagy-related gene *(ATG)16L1*.[41] *HLA-B27* is the most common gene associated with SpA and especially significantly more present in axial SpA patients compared with peripheral SpA. Additionally, the endoplasmic reticulum aminopeptidase *(ERAP)1* and cytokine genes including those involved in the Th-17 pathway have been identified in SpA patients as well.[39]

Different Genome Wide Association studies (GWAS) describe the genetic overlap between IBD and SpA and the most significant associations have been found concerning the *HLA-B27, IL23R, ERAP1/2* and Proteasome assembly chaperone *(PSMG)1/ATG5* genes.[42] *HLA-B27* belongs to the class I major histocompatibility heavy chain complex (MHC HC) class I on chromosome 6 and presents antigenic peptides to T-cells. Previous performed studies evaluated the presence of *HLA-B27* and the risk of developing isolated radiographic sacroiliitis or AS in IBD patients. Both study groups concluded that isolated sacroiliitis was not related with the presence of *HLA-B27*, while AS was associated with the presence of *HLA-B27* in 25-75% of the IBD patients. This risk was even more increased in CD patients with the presence of both ileal and colonic inflammation, implying the importance of the extension of the inflammation.[43-44] Another study determined the presence of the MHC class I chain-like gene A (*MICA*) in CD patients and patients with peripheral arthritis, subdivided into two subtypes; type 1 (oligoarticular) or type 2 (polyarticular). *MICA* interacts with T-cells of the intestinal immune stystem and induces cellular activation in conditions of cellular stress. This gene is in tight linkage disequilibrium with *HLA-B* (including *HLA-B27* and *HLA-B44*) located on chromosome 6. Patients with a *HLA-B44* or *HLA-27* genotype were at risk of developing CD or AS.[45] An association was found in patients with polyarticular peripheral arthritis between the MICA*008 allele and the presence of *HLA-B44*. Furthermore, there was an association between MICA*007, *HLA-B27* and having oligoarticular peripheral arthritis. In IBD patients, no association was described between *MICA* and CD. However, they found a link between the presence of the MICA*007 allele and UC.[46-47]

The *ATG16L1*, immunity-related GTPase family M (*IRGM*) and microtubule-associated proteins 1A/1B light chain (*MAP1LC)3A* genes are involved in autophagy in response to intracellular pathogens. Ciccia et al. determined the association of the expression of the *ATG16L1, IRGM, MAP1LC3A* genes and increased IL-23p19 mRNA levels in the ileum of both CD and AS patients with chronic inflammation in the intestine. Furthermore, misfolded HLA-B27 accumulation was present in the intestine of patients with AS based on the presence of free heavy chains (HCs) co-localized with a lack of E3 ubiquitin-protein ligase (SYVN1). SYNV1 encodes the protein involved in endoplasmic reticulum (ER)-associated degradation and removes unfolded proteins, increased during ER stress.[48-49]

Besides HLA-B27 involvement in SpA and IBD, the IL-23/Th-17 pathway is present in both diseases. IL-23 stimulates the differentiation of Th17. Binding of the IL-23 to the *IL-23R* complex stimulates the *JAK2* gene.[41,50] This gene transduces cytokine induced signals and activate *STAT* genes via the *JAK/STAT* pathway. This pathway results in DNA transcription and the expression of genes involved in immunity, proliferation, differentiation and apoptosis.[51] *STAT3* and *STAT4* both affect the Th-17 pathway in AS independently of *IL-23R* and the association between *STAT3, STAT4* and the Th-17 pathway has been described in the literature as a component of the common genetic pathway between AS and IBD patients.[52-54] *JAK2* seems only associated with CD, but not with AS.[52]

Davidson et al. described also the association of *ERAP1* and the development of AS patients. *ERAP1* is responsible for the processing of peptides within the endoplasmic reticulum to optimal length for MHC class I presentations and the cell surface receptors for pro-inflammatory cytokines.[55] Additionally, Tsui et al. reported that the combination of having the *ERAP1* and *HLA-B27* gene provides the most increased disease risk factor for the development of AS.[56] SNP rs2549794 in the *ERAP2* gene has been reported in the literature as a predisposing factor the presence of CD.[57]

The Fc receptor-like 3 (*FCRL3*) gene encodes the FCRL3 protein that also may play a role in the regulation of the immune system of IBD patients and mutations have been associated with rheumatoid arthritis (RA).[58] The presence of this gene is recently described in CD patients with peripheral joint complaints. Especially the AA genotype at -110G>A was correlated with both peripheral arthritis and arthralgia, although this association was less strong for arthralgia

probably due to subjective clinical diagnosis of arthralgia or the different pathophysiology between arthritis and arthralgia.[59]

NOD2, also known as *CARD15* is a gene located on chromosome 16. *NOD2* identifies peptidoglycans from bacterial cell wall components and stimulates an uncontrolled immune reaction to enteric bacteria.[60] Ferreirós-Vidal et al. determined whether mutations in the *NOD2* gene were associated with CD and AS and concluded that this gene did not contribute to the development of AS, indicating that differences are present between AS and CD patients.[61] This discrepancy may be caused by different bacteria involved or the type of cytokine response in the disease process. However, Peeters et al. described that *CARD15* variants were a significant predictor for developing sacroiliitis in CD patients.[62]

INTESTINAL MICROBIOME

The effects of the intestinal microbiota and the presence of inflammation is a recurring topic in present research. Microbiota in the intestine is described as the microbiome. Microbiota is acquired after birth and may be influenced by early infection, parenteral nutrition or antibiotic use in infancy and may induce autoimmune diseases such as SpA-related diseases including arthropathies in IBD. In CD, loss of clostridial commensals including Faecalibacterium and Roseburia which promotes gut homeostasis, have been found to be associated with active inflammation in the intestine.[63] Previous studies in IBD showed the association of Escherichia coli (E. coli) and the presence of this inflammatory disease.[64-65] Changes of intestinal bacteria may change the mucosa leading to an increase of antigen and immune response. Dorofeyev et al. identified that different bacteria including the Enterobacter, Staphylococcus, Klebsiella and Proteus were more often present in UC patients with joint complains compared with UC patients without joint complaints and healthy controls. In approximately 95% of the UC patients with joint complaints two or more types of bacteria were present in the bowel.[64] Furthermore, the IgG response against the outer membrane proteins of the Klebsiella was detectable in AS patients.[65]

SEROLOGY

Previous research has shown the existence of antibodies in the serum in both IBD and SpA patients and demonstrates the common pathophysiology. Wallis et al. examined the presence of different serological antibodies including anti-Saccharomyces cerevesiae (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-Eschericia coli outer membrane porin C (anti-OmpC) and anti-flagellin (anti-CBir1) in IBD and AS patients. ASCA is an antibody influencing the cell wall of the yeast Saccharomyces cerevisiae, ANCA is directed against antigens in the cytoplasm of neutrophil granulocytes and monocytes. IBD patients with AS showed a higher positivity rate of these biomarkers compared with AS patients and patients with back pain only. In addition, positivity rates for anti-CBir1 and ANCA were higher in AS patients compared with patients with back pain, but anti-OmpC levels did not differ between these two groups.[66] Feces calprotectein (fCAL) is a protein and can be detected in the stool of IBD patients as a result of neutrophil migration in the gut due to inflammation. Levels of fCAL correlate with the degree of gut inflammation. Increased fCAL levels have been seen in AS patients without signs or symptoms of IBD. Furthermore, a correlation has been found between fCAL-positive AS patients and IBD specific serological biomarkers including ANCA, anti-CBir1, anti-OmpC, ASCA IgG and IgA and thus suggest the possible genetic link between IBD and AS patients whose disease might me induced by subclinical bowel inflammation.[67-71] So far, there is no clinical value to detect RA biomarkers including IgM rheumatoid factor (IgM-RF), IgA-RF, anti-cyclic citrullinated peptide 2 (anti-CCP2), anti-cyclic citrullinated peptide 3.1 (anti-CCP3.1) and anti-carbamylated protein (anti-CarP) in IBD patients with arthropathies.[72] This implies that the immuno-pathogenesis of arthropathies in IBD differs from RA patients.

ENVIRONMENT

The development and presence of IBD is not only due to immunological, genetic, microbiotical and serological factors, but comprises also environmental aspects. The worldwide increase of IBD, also in countries where IBD previously was considered uncommon, indicates the effect of the environment on the development of the disease for example due to industrial revolution causing changes in lifestyle and air pollution. Thia et al. assessed that NO2 exposure was correlated with an increased risk of CD, while SO2 was correlated with an increase of UC.[73] In SpA patients, SO2 was associated with a SpA

disease activity outburst.[74] Zeboulon-Ktorza et al. determined dust exposure as an environmental factor relating with an increased Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a validated scoring system applicable for AS patients to assess patient reported disease activity.[75]

The classic environmental risk factor for developing CD is smoking and the literature has shown that CD patients who stopped smoking encountered less CD activity within 1 year. In contrast to CD, cigarette smoking seems to be protective for the development of UC. [76-77] Also in SpA patients, smoking increases the disease activity and worsens radiographic outcomes.[78]

The active variant of vitamin D (1alpha,25-dihydroxyvitamin D3 (1,25[OH]$_2$D$_3$)) appears to have an immunologic role on the innate immune system by the increased expression of inflammatory cytokines in the colon leading to colitis.[79-80] Patients with early diagnosed axial SpA reported severe vitamin D deficiency. This vitamin D deficiency was associated with disease activity and the existence of the metabolic syndrome.[81]

Furthermore, an association has been found in the literature between stress and an increased IBD disease activity.[82-83] Stress seems also to be a likely triggering factor for the development of SpA.[75] Knowing these environmental factors influencing the presence of the disease or the disease activity, may be interesting for treatment options in the clinic.

CONCLUSION

In summary, this review provides an insight of the common pathophysiology and identifies the complex interplay between IBD and SpA. Several suggestions for the linkage between gut and joint inflammation have been put forward including the efficacy of anti-TNF therapy on clinical and laboratory outcomes in both SpA and IBD patients and the presence of the IL-23/IL-17 pathway in both diseases; the comparable up-regulation of IL-23 synthesis and the stimulation of Th-17 differentiation by IL-23 increase, activating *STAT3* and *STAT4* genes via the *JAK/STAT* pathway in both IBD and AS causing over-activation of the immune response resulting in apoptosis and chronic inflammation. Furthermore, the association between the presence of *HLA-B44* and *HLA-B27* and CD and/or AS was assessed. Also, increased ANCA, ASCA, anti-OmpC and

anti-CBir1 biomarkers were found in the serum of IBD patients with AS compared with AS patients only. In addition, increased serum levels for anti-CBir1 and ANCA were determined in AS patients compared with healthy controls indicating the presence of IBD serological biomarkers in AS patients. In both IBD and SpA, smoking, stress and dust exposure seemed to be factors associated with the presence of these inflammatory diseases. This review provides clinical, genetic, immunological, serological and environmental evidence supporting the overlap between gut and joint inflammation.

REFERENCES

1. Zhang Y, Li Y. Inflammatory bowel disease: Pathogenesis. World J Gastroenterol 2014;20(1):91-99.
2. Tremaine WJ. Diagnosis and Treatment of Indeterminate Colitis. Gastroenterol Hepatol 2011;7(12):826–28.
3. Torres J, Mehandru S, Colombel J, et al. Crohn's disease. Lancet 2017;389:1741–55.
4. Torres J, Mehandru S, Colombel J, et al. Ulcerative colitis. Lancet 2017;389:1756–70.
5. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.
6. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol 2010;6:339-46.
7. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860-65.
8. Van Erp SJH, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2015;9(3):276-83.
9. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:2217-37.
10. Stolwijk C, van Onna M, Boonen A, et al. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. Arthritis Care Res 2016;68(9):1320-31.
11. 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.
12. 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.
13. Brophy S, Pavy S, Lewi P, et al. Inflammatory eye, skin, and bowel disease in spondyloarhtritis: genetic, phenotypic and environmental factors. J Rheumatol 2001;28:2667-73.
14. Van Praet L, Van den Bosch FE, Jacques P, et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. Ann Rheum Dis 2013;72:414–17.
15. Ciccia F, Bombardieri M, Principato A, et al. Overexpression of interleukin-23, but not interleukin-17, as an immunologic signature of subclinical intestinal inflammation in ankylosing spondylitis. Arthritis Rheum 2009;60(4):955-65.
16. Mielants H, Veys EM, Cuvelier C, et al. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. J Rheumatol 1995;22:2273–78.
17. Bouwmeester T, Bauch A, Ruffner H, et al. A physical and functional map of the human TNF-alpha/NF-kappa B signal transduction pathway. Nat Cell Biol 2004;6(2):97-105.
18. Faustman DL, Davis M. TNF Receptor 2 and Disease: Autoimmunity and Regenerative Medicine. Front Immunol 2013;23(4):478.
19. Ackermann C, Kavanaugh A. Tumor necrosis factor as a therapeutic target of rheumatologic disease. Expert Opin Ther Targets 2007;11(11):1369-84.
20. Rollins BJ, Yoshimura T, Leonard EJ, et al. Cytokineactivated human endothelial cells synthesize and secrete a monocyte chemoattractant, MCP-1/JE. Am J Pathol 1990;136:1229–33.

21. Koch AE, Harlow LA, Haines GK, et al. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. J Immunol 1994;152(8):4149–56.
22. Kontoyiannis D, Pasparakis M, Pizarro TT, et al. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. Immunity 1999;10:387-98.
23. Westlund KN, Zhang L, Ma F, et al. Chronic Inflammation and Pain in a TNFR (p55/p75-/-) Dual Deficient Murine Model. Transl Res 2012;160(1):84–94.
24. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gatroenterol Hepatol 2015;12(9):537-45.
25. Den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis 2002;61(4):311-18.
26. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346(18):1349–56.
27. Casanova MJ, Chaparro M, García-Sánchez V, et al. Evolution After Anti-TNF Discontinuation in Patients With Inflammatory Bowel Disease: A Multicenter Long-Term Follow-Up Study. Am J Gastroentol 2017;112(1):120-31.
28. Baraliakos X, Listing J, Brandt J, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7(3):R439-44.
29. Pène J, Chevalier S, Preisser L, et al. Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. J Immunol 2008;180:7423-30.
30. Gheita TA, El Gazzar II, El-Fishawy HS, et al. Involvement of IL-23 in enteropathic arthritis patients. Clin Rheumatol 2014;33:713–17.
31. Ahern PP, Izcue A, Maloy KJ, et al. The interleukin-23 axis in intestinal inflammation. Immunol Rev 2008;226:147-59.
32. Dmowska-Chalaba J, Kontny E. Inflammatory bowel disease-related arthritis – clinical evaluation and possible role of cytokines. Reumatologia 2015;53(5):236-42.
33. Ciccia F, Accardo-Palumbo A, Rizzo A, et al. Evidence that autophagy, but not the unfolded protein response, regulates the expression of IL-23 in the gut of patients with Ankylosing Spondylitis and subclinical gut inflammation. Ann Rheum Dis 2014;73(8):1566–74.
34. Singh R, Aggarwal A, Misra R. TH1/TH17 cytokine profiles in patients with reactive arthritis/undifferentiated spondyloarthropathy. J Rheumatol 2007;34:2285–90.
35. Sofen H, Smith S, Matheson RT, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol 2014;133:1032–40.
36. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med 2015;373:2534-48.
37. Gaffen SL, Jain R, Garg AV, et al. The IL-23 IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 204;14:585–600.
38. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature 2011;474(7351):307–17.
39. Reveille JD. The genetic basis of spondyloarthritis. Ann Rheum Dis 2011;70:44-50.
40. Bjarnason I, Helgason KO, Geirsson AJ, et al. Subclinical intestinal inflammation and sacroiliac changes in relatives of patients with ankylosing spondylitis. Gastroenterology 2003;125:1598–1605.

41. Uniken Venema WT, Voskuil MD, Dijkstra G, et al. The genetic background of inflammatory bowel disease: from correlation to causality. J Pathol 2017;241(2):146-58.
42. Lees CW, Barrett JC, Parkes M, et al. New IBD genetics: common pathways with other diseases. Gut 2011;60(12):1739-53.
43. Peeters H, Vander Cruyssen B, Mielants H, et al. Clinical and genetic factors associated with sacroiliitis in Crohn's disease. J Gastroenterol Hepatol 2008;23(1):132-37.
44. Orchard TR, Holt H, Bradbury L, et al. The prevalence, clinical features and association of HLA-B27 in sacroiliitis associated with established Crohn's disease. Aliment Pharmacol Ther 2009;29(2):193-97.
45. Purrmann J, Zeidler H, Bertrams J, et al. HLA antigens in ankylosing spondylitis associated with Crohn's disease. Increased frequency of the HLAphenotype B27,B44. J Rheumatol 1988;15(11):1658-61.
46. Orchard TR, Thiyagaraja S, Welsh KI, et al. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. Gastroenterology 2000;118(2):274-78.
47. Orchard TR, Dhar A, Simmons JD, et al. MHC class I chain-like gene A (MICA) and its associations with inflammatory bowel disease and peripheral arthropathy. Clin Exp Immunol 2001;126(3):437-40.
48. Ciccia F, Accardo-Palumbo A, Rizzo A, et al. Evidence that autophagy, but not the unfolded protein response, regulates the expression of IL-23 in the gut of patients with ankylosing spondylitis and subclinical gut inflammation. Ann Rheum Dis 2014;73(8):1566-74.
49. Burr ML, Cano F, Svobodova S, et al. HRD1 and UBE2J1 target misfolded MHC class I heavy chains for endoplasmic reticulum-associated degradation. Proc Natl Acad Sci USA 2011;108(5):2034-39.
50. Wong RH, Wei JC, Huang CH, et al, Association of IL-12B genetic polymorphism with the susceptibility and disease severity of ankylosing spondylitis. J Rheumatol 2012;39(1):135-40.
51. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci 2004;117:1281-83.
52. Davidson SI, Liu Y, Danoy PA, et al. Association of STAT3 and TNFRSF1A with ankylosing spondylitis in Han Chinese. Ann Rheum Dis 2011;70(2):289-92.
53. Danoy P, Pryce K, Hadler J, et al. Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. PLoS Genet 2010;6(12):e1001195.
54. Martínez A, Varadé J, Márquez A, et al. Association of the STAT4 gene with increased susceptibility for some immune-mediated diseases. Arthritis Rheum 2008;58(9):2598-602.
55. Davidson SI, Wu X, Liu Y, et al. Association of ERAP1, but not IL23R, with ankylosing spondylitis in a Han Chinese population. Arthritis Rheum 2009;60(11):3263-68.
56. Tsui FW, Tsui HW, Akram A, et al. The genetic basis of ankylosing spondylitis: new insights into disease pathogenesis. Appl Clin Genet 2014;7:105-15.
57. Castro-Santos P, Moro-García MA, Marcos-Fernández R, et al. ERAP1 and HLA-C interaction in inflammatory bowel disease in the Spanish population. Innate Immun 2017;23(5):476-81.
58. Lin X, Zhang Y, Chen Q. FCRL3 gene polymorphisms as risk factors for rheumatoid arthritis. Hum Immunol 2016;77(2):223-29.
59. Mendoza JL, Lana R, Martin MC, et al. FcRL3 gene promoter variant is associated with peripheral arthritis in Crohn's disease. Inflamm Bowel Dis 2009;15(9):1351-57.
60. Punchard NA. Overview: Nod2, cause of, or contributor to, Crohn's disease. Curr Opin Investig Drugs 2001;2(10):1378-81.
61. Ferreirós-Vidal I, Amarelo J, Barros F, et al. Lack of association of ankylosing spondylitis with the most common NOD2 susceptibility alleles to Crohn's disease. J Rheumatol 2003;30(1):102-4.

62. Peeters H, Vander Cruyssen B, Laukens D, et al. Radiological sacroiliitis, a hallmark of spondylitis, is linked with CARD15 gene polymorphisms in patients with Crohn's disease. Ann Rheum Dis 2004;63(9):1131-34.
63. Asquith M, Elewaut D, Lin P, et al. The role of the gut and microbes in the pathogenesis of spondyloarthritis. Best Pract Res Clin Rheumatol 2014;28(5):687–702.
64. Dorofeyev AE, Vasilenko IV, Rassokhina OA. Joint extraintestinal manifestations in ulcerative colitis. Dig Dis 2009;27(4):502-10.
65. Madhavan R, Porkodi R, Rajendran CP, et al. IgM, IgG, and IgA response to enterobacteria in patients with ankylosing spondylitis in southern India. Ann NY Acad Sci 2002;958:408-11.
66. Wallis D, Asaduzzaman A, Weisman M, et al. Elevated serum anti-flagellin antibodies implicate subclinical bowel inflammation in ankylosing spondylitis: an observational study. Arthritis Res Ther 2013;15(5):R166.
67. Matzkies FG, Targan SR, Berel D, et al. Markers of intestinal inflammation in patients with ankylosing spondylitis: a pilot study. Arthritis Res Ther 2012;14(6):R261.
68. De Vries M, van der Horst-Bruinsma I, van Hoogstraten I, et al. pANCA, ASCA, and OmpC antibodies in patients with ankylosing spondylitis without inflammatory bowel disease. J Rheumatol 2010;37(11):2340-44.
69. Mundwiler ML, Mei L, Landers CJ, et al. Inflammatory bowel disease serologies in ankylosing spondylitis patients: a pilot study. Arthritis Res Ther 2009;11(6):R177.
70. Török HP, Glas J, Gruber R, et al. Inflammatory bowel disease-specific autoantibodies in HLA-B27-associated spondyloarthropathies: increased prevalence of ASCA and pANCA. Digestion 2004;70(1):49-54.
71. Locht H, Skogh T, Wiik A. Characterisation of autoantibodies to neutrophil granule constituents among patients with reactive arthritis, rheumatoid arthritis, and ulcerative colitis. Ann Rheum Dis 2000;59(11):898-903.
72. Van Erp SJ, Verheul MK, Levarht EW, et al. Short article: Absence of serological rheumatoid arthritis biomarkers in inflammatory bowel disease patients with arthropathies. Eur J Gastroenterol Hepatol 2017;29(3):345-48.
73. Thia KT, Loftus EV Jr, Sandborn WJ, et al. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 2008;103:3167-82.
74. Vidotto JP, Pereira LA, Braga AL, et al. Atmospheric pollution: influence on hospital admissions in paediatric rheumatic diseases. Lupus 2012;21(5):526-33.
75. Zeboulon-Ktorza N, Boelle PY, Nahal RS, et al. Influence of environmental factors on disease activity in Spondyloarthritis: A Prospective Cohort Study. J Rheumatol 2013;40(4):469-75.
76. Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Ther 1999;13:1403-11.
77. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. Am J Gastroenterol 2012;107:1399-1406.
78. Dougados M, Demattei C, van den Berg R, et al. Rate and predisposing factors for sacroiliac joint radiographic progression after a two-year follow-up period in recent-onset spondyloarthritis. Arthritis Rheumatol 2016;68(8):1904-13.
79. Cantorna MT, Mahon BD. D-hormone and the immune system. J Rheumatol 2005;76:11-20.
80. Froicu M, Cantorna MT. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. BMC Immunol 2007;8:5.
81. Hmamouchi I, Paternotte S, Molto A, et al. Vitamin D, disease activity and comorbidities in early spondyloarthritis. Clin Exp Rheumatol 2016;34(3):396-403.

82. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol 2009;104:1298-1313.
83. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 2008;57:1386-92.

CHAPTER 3

Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow up study

S.J.H. van Erp*, L.K.P.M. Brakenhoff*, F.A. van Gaalen, R. van den Berg, H.H. Fidder, H.W. Verspaget, T.W.J Huizinga, R.A. Veenendaal, R. Wolterbeek, D. van der Heijde, A.E. van der Meulen-de Jong, D.W. Hommes

Journal of Crohns and Colitis, 2016
** Shared first authorship*

ABSTRACT

Background: 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 one 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 ASAS criteria for axial and peripheral SpA were fulfilled in 12.3% of patients, with 9.7% (n=15) receiving a rheumatologic diagnosis of arthritis. During the 12-month follow-up, the majority of the amount of patients reporting joint/back pain remained stable.

Conclusion: 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.

INTRODUCTION

Arthropathies are the most common extra-intestinal manifestations (EIMs) 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 rheumatologic standards, thus allowing appropriate multi-disciplinary 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 included patients with less than five joints involved, evidence of joint swelling and acute, but self-limiting attacks. Type 2 (polyarticular) peripheral arthritis included 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 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 characterized by inflammation of the spine and the sacroiliac (SI) joints. This often results in pain and/or stiffness of the spine and neck. Besides, inflammation may affect other regions including the peripheral joints, tendons, eyes, skin and/or gut.

In order to develop a multi-disciplinary care pathway for IBD patients with joint complaints, we rigorously characterized 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 com-

plaints 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.

METHODS

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 last year, (3) current pJTC (pain and/or joint swelling) and (4) pJTC during the last 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 radiologic proven sacroiliitis were directly referred for rheumatologic care. All IBD patients without joint/back pain during the previous year served as controls and were also invited to attend the multidisciplinary clinic. To avoid that high inclusion rates would influence the quality of patient care and since only one clinical researcher was able to perform physical and rheumatologic examination, 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 prior to study enrolment.

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 one 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 of all participants on extra-intestinal manifestations were collected, 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 rheumatologic 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 was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[10] and the Bath Ankylosing Spondylitis Functional Index (BASFI).[11] Laboratory assessments included ESR and CRP. 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 radiographs of the most painful peripheral joints were performed in patients with joint/back pain.

Following the baseline assessment, patients were categorized 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 and/or pJTC during the previous year.

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 was 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 was 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]

SpA classifications

In short, the *Amor criteria* for SpA consist of a scoring system of 8 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 asymmetric 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 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 asymmetric 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 for further details).

Statistics

Continuous variables were described with mean ± standard deviation (SD) and categorical variables as proportions with percentages. T-tests were used for comparing continuous variables among the two study groups and Fisher 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 anal-

yses were performed for several variables, including age, gender, type of IBD, IBD-associated surgery, active IBD (HBI or SCCAI > 4), 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 (e.g. 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 as dependent variables. All analyses were performed using SPSS version 20. P-values ≤0.05 were considered significant.

RESULTS

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 highest in CD (65%) compared to 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 informed consent and attended the multidisciplinary clinic, of whom 155 (60.1%) were assigned to the study group with joint/back pain, while 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 to patients with IBD without joint/back pain. The Montreal classification did not reveal subtypes

more prone for 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, while 80.0% of patients reported involvement of more than one joint. At physical examination, 98 (63.2%) patients had ≥ 1 tender joint(s), while 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 rheumatologic examination or on the radiographs were referred to the rheumatologist. Based on physical examination performed by the rheumatologist, fifteen 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, 1 (0.7%) patient was diagnosed with dactylitis, 1 (0.7%) patient with enthesitis and 2 (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 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 to pJTC patients without CBP: 1.7 (SD 0.9) vs. 1.4 (SD 0.8), p=0.03.

Univariate analysis showed that CD (p=0.002), female (p=0.001), smoking (p=0.002), IBD disease activity (p<0.001), cutaneous manifestations (p=0.02) and acute anterior uveitis (p=0.003) were associated with an increased odds ratio (OR) for joint/back pain (Table 3). In the multivariate analysis, the variables female (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.

Classification

Overall, IBD patients with CBP had on average 1.7 SpA features, pJTC patients 1.4, while 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, while 63 (40.6%) patients fulfilled any of the SpA criteria sets: 32 (20.6%) patients fulfilled the Amor criteria, 52 (33.5%) patients fulfilled the ESSG criteria, including 37 (71.2%) in the inflammatory back pain arm, 10 the peripheral arm, and 5 both arms. Nineteen (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 4 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 to those who did not fulfil any of the SpA criteria sets (data not shown).

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, while 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 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 to 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 to 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 $p \leq 0.05$). 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 from 0.96-1.00, $p \leq 0.05$). Gender had no significant effect.

DISCUSSION

Since gastroenterologists are not used to the diagnosis and management of joint/back pain, a multidisciplinary approach in co-operation 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 characterized these complaints in depth. In our cohort, IBD patients reporting joint/back pain were more likely to be diagnosed with CD, were more commonly female, smokers and showed more often cutaneous manifestations and acute anterior uveitis compared to 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 with pain and disease activity of the spine and peripheral joints over time. Although joint/back pain is frequently encountered in IBD patients[1-3,14,20-21], 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[23-25] 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 standardized 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 the ESSG criteria compared to 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 of criteria. 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 recognized as a 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 that can be utilized 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 categorized into SpA and non-SpA. This is also emphasized 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 and 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.[32-34] 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 rheumatologic 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.

REFERENCES

1. De Vlam K, Mielants H, Cuvelier C, et al. 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, et al. 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;42:387-91.
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, et al. 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;21:2281-85.
12. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;8:514.
13. Walmsley RS, Ayres RC, Pounder RE, et al. 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;19:141–48.
15. Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. Rev Rheum Mal Osteoartic 1990;57:85-89.
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;27:361-68.
20. Palm Ø, Moum B, Jahnsen J, et al. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). Rheumatology 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;48-49:128-33.
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;41:451-58.
25. Thia K, Faubion WA Jr, Loftus EV Jr, et al. 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(3):276-83.
27. Van den Berg R, de Hooge M, van Gaalen F, et al. 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 2013;52:1492-99.
28. Van den Berg R, van Gaalen F, van der Helm-van Mill A, et al. Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis cohort. Ann Rheum Dis 2012;71:1366-69.
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(3):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(1):56-62.
34. Häkkinen A, Sokka T, Kautainen H, et al. 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(8):910-16.
35. Wendling D, Vuitton L, Koch S, et al. Spondyloarthritis and the gut: A new look. Joint Bone Spine 2015;82(2):77-79.

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;13(6):1042-50.
37. Visser H, le Cessie S, Vos K, et al. 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. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015;74(7):1327-39.

TABLES AND FIGURES

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

	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			
Location CD, n (%)	*n=121*	*n=65*	0.06
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-structuring/penetrating	77 (63.6)	32 (49.2)	
B2 structuring	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

[a] Family history SpA: AS, 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.

Table 2. Characteristics of 155 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 (%)				0.61
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 (MCP-PIP-DIPs)	-	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

[a] All confirmed by a specialist; [b] Based on one of the different SpA criteria.

Table 3. Logistic regression analyses of IBD patients, with the presence of arthropathies as the dependent variable.

		Univariate		Multivariate	
Variable	**n**	**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	97				
Female (ref)	158	2.47 (1.46-4.16)	0.001	1.97 (1.10-3.53)	0.02
Type of IBD					
UC	69				
CD (ref)	186	1.92 (1.10-3.36)	0.02	1.25 (0.66-2.35)	0.51
Smoking					
No	195				
Yes (ref)	60	2.91 (1.48-5.73)	0.002	2.28 (1.10-4.75)	0.03
Active IBD disease [a]					
No	153				
Yes (ref)	103	4.61 (2.57-8.26)	<0.001	4.07 (2.23-7.45)	<0.001
IBD-related surgery					
No	148				
Yes (ref)	107	1.22 (0.73-2.04)	0.44		
Cutaneous manifestations [b]					
No	221				
Yes (ref)	34	2.80 (1.17-6.71)	0.02	1.74 (0.66-4.56)	0.26
Ocular manifestation [c]					
No	228				
Yes (ref)	27	3.14 (1.15-8.6)	0.03	1.83 (0.61-5.48)	0.28
Family history SpA [d]					
No	181				
Yes (ref)	74	1.0 (0.57-1.74)	1.00		

[a] HBI or SCCAI score > 4; [b] Cutaneous manifestations: psoriasis, erythema nodosum, pyoderma gangrenosum; [c] Ocular manifestation: acute anterior uveitis; [d] Family history SpA (SpondyloArthritis); ankylosing spondylitis, reactive arthritis, psoriasis, IBD, uveitis all according to the definition of the ASAS criteria.

Figure 1. Patient inclusion flow chart.

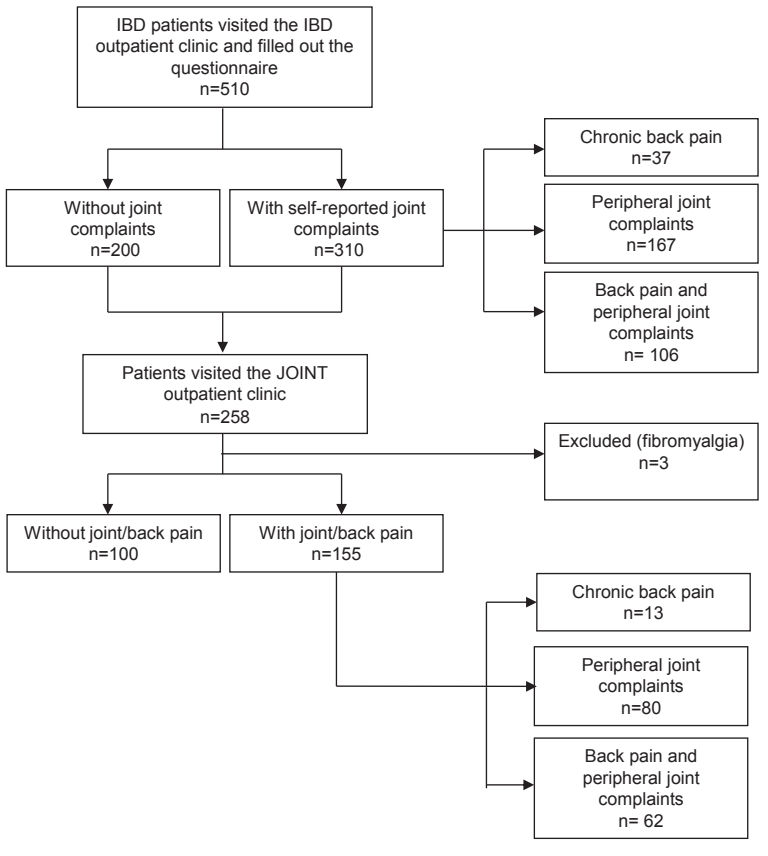
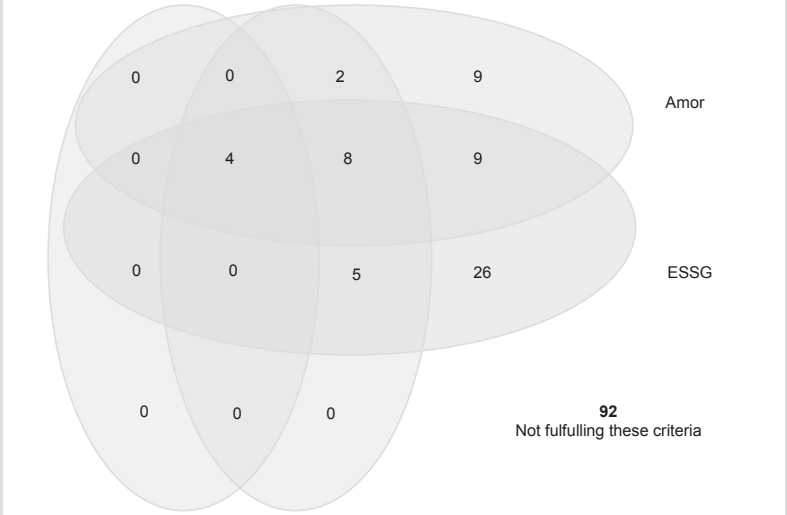


Figure 2. Venn diagram representing the overlap between the various classification criteria for SpA.



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]

Figure 3. Follow-up IBD patients.

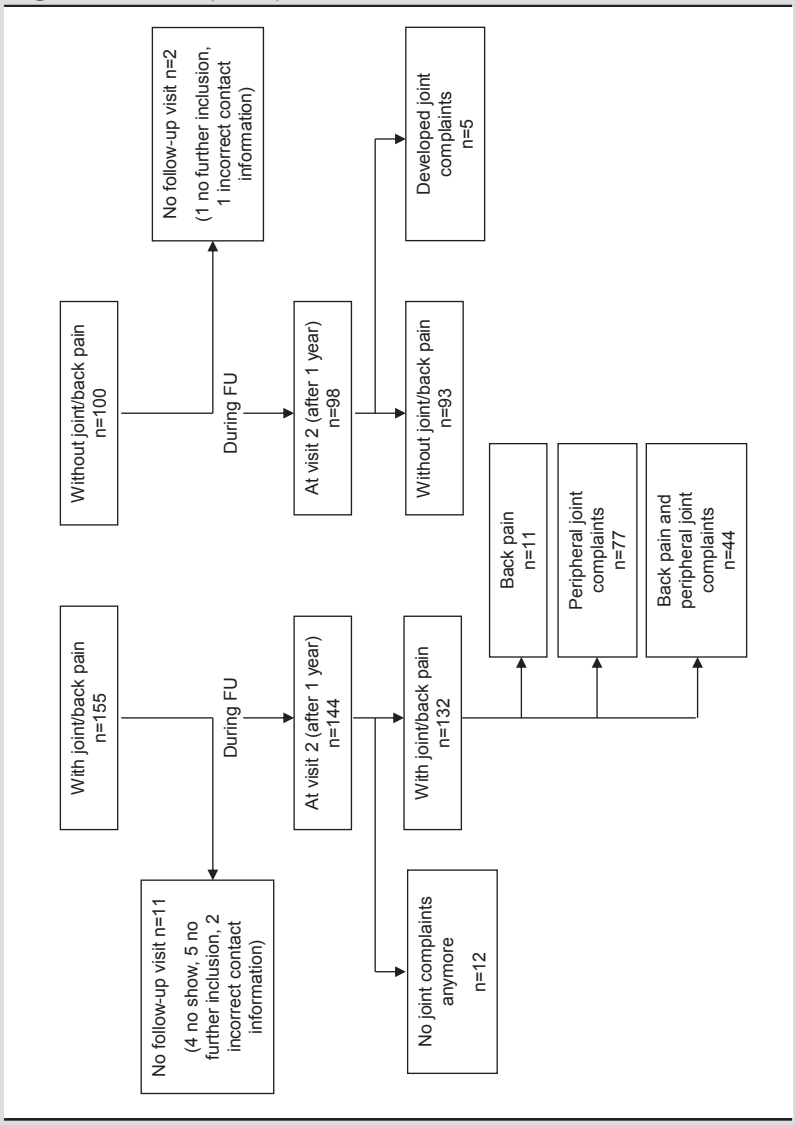
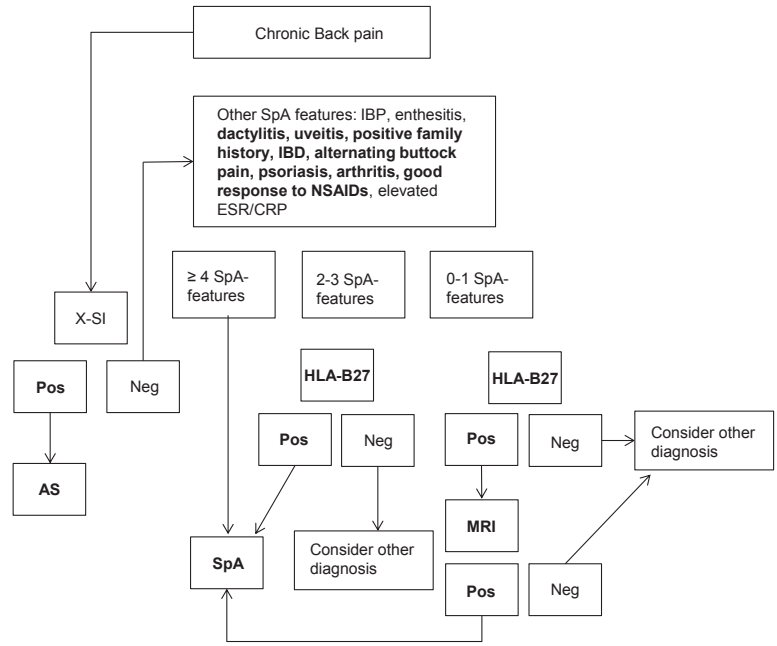


Figure 4. Proposal for the referral algorithm for suspected axial SpA in patients with IBD.



The first step for the gastroenterologist is to refer all patients with 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 SI joints is recommended as first imaging method, but in certain cases, such as young patients and those with a short symptom duration, 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 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]

CHAPTER 4

Absence of serological rheumatoid arthritis biomarkers in inflammatory bowel disease patients with arthropathies

S.J.H. van Erp, M.K. Verheul, E.W.N. Levarht, J.J. van der Reijden, D. van der Heijde, F.A. van Gaalen, D.W. Hommes, G.L. Norman, Z. Shums, M. Mahler, H.W. Verspaget, L.A. Trouw, A.E. van der Meulen-de Jong

European Journal of Gastroenterology and Hepatology, 2016

ABSTRACT

Background: Biomarkers that are associated with future progression to rheumatoid arthritis (RA) and joint destruction have previously been discovered in patients with arthralgia. The present study examined these RA biomarkers in inflammatory bowel disease (IBD) patients with arthropathies.

Methods: Sera from 155 IBD patients with and 99 IBD patients without arthropathies was analysed for IgM rheumatoid factor (IgM-RF), IgA-RF, anti-cyclic citrullinated peptide 2 (anti-CCP2), anti-cyclic citrullinated peptide 3.1 (anti-CCP3.1) and anti-carbamylated protein (anti-CarP) antibody positivity using enzyme-linked immunosorbent assays (ELISA). The prevalence of these autoantibodies in IBD patients was compared to the prevalence in RA patients.

Results: No differences were found in biomarker positivity between IBD patients with and without arthropathies. Significantly more biomarker positivity ($p<0.001$) was observed in RA patients compared with IBD patients with arthropathies. Also, smoking turned out to be significantly associated with IgM-RF and IgA-RF positivity.

Conclusion: Our findings suggest that there is no apparent clinical value to detect RA biomarkers in serum of IBD patients to help to identify arthropathies.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by destructive polyarthritis, which leads to disability and increased mortality.[1] Early diagnosis and initiation of treatment is important in RA, since a considerable number of patients develop irreversible joint damage shortly after disease onset.[2-3]

Serological biomarkers, including rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies (anti-CarP), have previously been reported to be important diagnostic markers and predictive factors for the development of RA at an early stage.[4-10] RF is an autoantibody directed against the Fc region of immunoglobulin (Ig)G and commonly detected in RA, but can also be positive in patients with other autoimmune and non-autoimmune diseases as well as in healthy individuals.[4] ACPA are often detected using assays based on cyclic citrullinated peptides (CCP), such as the CCP2 and CCP3 assays. Citrullination is the conversion of the amino acid Arginine into Citrulline, mediated by peptidylarginine deiminase (PAD).[5-6] Anti-CCP antibodies are highly specific (up to 99%) for RA, but less sensitive compared to RF. Testing for RF and ACPA simultaneously, has been suggested to improve sensitivity. Recently an anti-CCP3.1 assay was developed that detects both IgG and IgA anti-CCP antibodies to improve both sensitivity and specificity.[7] In addition, another autoantibody designated by Shi et al. as anti-CarP antibodies, has been described as a disease marker in RA patients and targets carbamylated proteins rather than citrullinated.[8] Carbamylation constitutes a posttranslational modification of lysine to homocitrulline under the influence of cyanate.[9] Increased carbamylation is related to chronic inflammatory conditions.[10] Anti-CarP antibodies are present in both anti-CCP positive and negative patients and may predict the development of RA, independently from anti-CCP antibodies.[11-13]

Inflammatory bowel disease (IBD) is associated with various extra-intestinal manifestations, including arthropathies with a prevalence of approximately 30%.[14] IBD-associated arthropathies can be subdivided into inflammatory (spondyloarthritis; SpA) based on the rheumatological ASAS criteria for axial and peripheral SpA and non-inflammatory (arthralgia) joint complaints.[15]

Although previous studies report a genetic link, with shared susceptibility genes between RA patients and arthropathies in IBD,[16] less is known about

the presence of serological RA biomarkers in IBD patients with arthropathies. Therefore, in the present study we examined the presence of RA biomarkers in IBD patients with arthropathies and compared biomarker positivity in these patients with IBD patients without arthropathies and RA patients.

METHODS

Study population

The inclusion procedure of IBD patients was as described previously.[15] Briefly, serum samples were collected from 254 IBD patients included in the JOINT study, a single-center prospective longitudinal study focused on IBD patients with and without arthropathies, performed at the department of Gastroenterology and Hepatology of the Leiden University Medical Center (LUMC), the Netherlands. Patients visiting the IBD outpatient clinic from July 2009 to February 2010, were asked to complete a questionnaire to assess the presence of joint complaints during the previous year. Patients with self-reported joint and/or back pain (n=155) were invited to attend the JOINT outpatient clinic. This clinic was established by the department of Gastroenterology and Hepatology and the department of Rheumatology to expand the knowledge of IBD joint complaints. All IBD patients without self-reported joint complaints served as controls (n=99). At the JOINT outpatient clinic, medical history and data on extra-intestinal manifestations (EIMs) were collected. In addition to routine physical examination, a rheumatologic examination was performed in all IBD patients, including a detailed assessment of the number of tender and swollen joints. Laboratory assessments included the erythrocyte sedimentation rate (ESR) and the C-Reactive Protein (CRP). HLA-B27 was only typed in patients with chronic back pain (CBP) and/or peripheral joint complaints. Of the 155 patients with self-reported arthropathies, 63 (40.6%) were classified according to the different SpA classification criteria as reported previously.[15] Of these patients, 19 (12.3%) patients fulfilled the ASAS criteria for axial and peripheral SpA, the most often used classification criteria in clinical trials and the most practical system with which to classify SpA.[15,17] Eventually in total 15 (9.6%) patients were diagnosed with arthritis by a rheumatologist (FvG).

For the current protocol, the presence of the different serological biomarkers in 147 RA patients from the early arthritis clinic (EAC) was used as a comparison. This inception cohort comprises patients with arthritis with a disease

duration of less than 2 years. After 1 year of follow-up a final diagnosis was established and for this measurement, only baseline samples were used of patients who were diagnosed with RA and fulfilled the 1987 criteria.[18] The study was approved by the institutional medical ethical committee of the LUMC and patients signed a written informed consent prior to study enrolment, including biobanking protocol.

Measurement of serologic biomarkers

Serum levels of IgM-RF, IgA-RF, anti-CCP2, anti-CCP3.1 and anti-CarP IgG and IgA were determined using enzyme-linked immunosorbent assay (ELISA); the cut-off values used for anti-CCP2 was 25.0 AU/ml. For anti-CarP antibodies the cut-off was established as the mean plus 2 x SD of 200 healthy controls, as before.[8] Cut-off levels of IgM-RF, IgA-RF and anti-CCP3.1 were 6.0 AU/ml, 6.0 AU/ml and 20.0 AU/ml according to the manufacturer's (Inova Diagnostics Inc., San Diego) recommendation. Positivity of IgM-RF, IgA-RF, anti-CCP2, anti-CCP3.1 and anti-CarP in IBD patients with arthropathies were compared with those without arthropathies and RA patients.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 software (IBM). Chi-square tests and Student's t-test for independent samples were used to compare the biomarker positivity in IBD patients with arthropathies with IBD patients without arthropathies and RA patients. Logistic regression analysis, with the different biomarkers as dependent variable, was performed to assess variables associated with a positive biomarker. Univariate analyses were performed for several variables including age, gender, type of IBD, IBD disease activity (Harvey Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI) > 4), smoking, arthritis (diagnosed by the rheumatologist) or SpA, classified according to the different SpA classification criteria.[15] Variables with a statistical level of $p<0.1$ in the univariate analysis were included in the multivariate analysis. A p-value ≤ 0.05 was considered as statistically significant.

RESULTS

Characteristics of the 254 patients with and without arthropathies are presented in Table 1. IBD patients with arthropathies were significantly more often diagnosed with Crohn's Disease (CD), more frequently female and smokers. No differences in biomarker positivity were found between IBD patients with and without arthropathies. Univariate analysis in all IBD patients showed that female gender (p=0.05, OR=0.5, 95%CI 0.25-0.99) and smoking (p=0.01, OR=2.4, 95%CI 1.21-4.55) were associated with a risk of having a positive IgM-RF antibody test. In the multivariate analysis, smoking (p=0.02, OR=0.44, 95%CI 0.22-0.85) remained independently associated with a positive IgM-RF test. In the univariate analysis for IgA-RF, smoking turned out to be significantly associated (p=0.03, OR=4.3, 95%CI 1.12-6.60) with a positivity for IgA-RF.

When a subdivision was made within the group of IBD patients with arthropathies based on CD and Ulcerative Colitis (UC), significantly more UC patients had a positive anti-CarP IgG antibody test (CD: 1 (0.8%) vs UC: 3 (8.8%), p=0.009). In addition, positivity of IgM-RF, IgA-RF, anti-CCP2, anti-CCP3.1, anti-CarP IgG and anti-CarP IgA in IBD patients with arthropathies were compared with RA patients. IBD patients with arthropathies were significantly less frequently positive for IgM-RF, anti-CCP2, anti-CCP3.1, anti-CarP IgA and anti-CarP IgG antibodies biomarkers (p<0.001) compared with the RA patients (Figure 1). When the 15 IBD patients with arthritis were compared with the 239 IBD patients without arthritis, none of the biomarkers were significantly more prevalent in the group of patients with both IBD and arthritis.

DISCUSSION

In the present study, RA biomarkers were assessed in IBD patients with and without arthropathies and the frequency of biomarker positivity was compared to RA patients. The RA markers were infrequently present in the IBD patients with no significant differences in positivity between IBD patients with and without arthropathies. A striking difference in autoantibody positivity was observed when comparing IBD patients with arthropathies to RA patients. In addition, as seen in RA, smoking seems to be related to IgM-RF and IgA-RF positivity in IBD.[19-20]

Although anti-CCP is highly specific for RA, previous studies have shown the occurrence of positive anti-CCP antibodies in other arthropathies such as psoriatic arthritis (PsA) and IBD patients.[21-24] Haga et al. concluded that the prevalence of anti-CCP IgA antibodies in IBD patients is low (1.2%), but significantly associated with arthritis and IgM-RF positivity. However, in studies of Papamichaels and Koutroubakis no significant association between the prevalence of anti-CCP positivity and IBD related arthropathies was found.[22-24] This is in accordance with the present study; in none of the IBD patients anti-CCP2 was detected and in 11 (6/155=3.8% with arthropathies and 5/99=5% without) IBD patients anti-CCP3.1 was present.

While the presence of anti-CCP2 and anti-CCP3.1 in IBD patients has been examined previously,[22-24] positivity for other possible arthropathy-related biomarkers has not been reported in IBD patients before. In the present study, besides the presence of anti-CCP2 and anti-CCP3.1, IgM-RF, IgA-RF and anti-CarP antibodies were assessed in the sera of IBD patients with and without arthropathies. In contrast to the increased sensitivity in RA patients achieved by combinations of these biomarkers, they did not add clinical value. Recently, Shi et al. reported that anti-CarP antibodies are the most sensitive antibodies that are present before RA becomes clinically apparent.[8] In our study anti-CarP was detected in only 4 (2.6%) IBD patients with arthropathies compared to 66 (42.6%) RA patients.

In the present study, smoking seems to be related with a positive IgM-RF and IgA-RF in IBD patients with arthropathies and supports the findings by Mikuls et al. in which current smokers were approximately twice as likely as never smokers to have increased IgA-RF concentrations. This association was most pronounced in the patients with more than 20 pack-years of exposure.[25]

An important strength of this study is the well-defined study cohort with all IBD patients classified thoroughly with or without SpA. Second, all different biomarkers known in RA patients were evaluated in this study design in IBD patients and compared with RA patients. A limitation of this study is the limited number of 15 patients with proven arthritis after rheumatologic examination although a total of 63 patients fulfilled one of the clinical SpA criteria. No difference in biomarker positivity was found between these 15 IBD patients with and 239 IBD patients without arthritis. Probably the number of in total 15 IBD patients diagnosed with arthritis was too small to make this difference.

Taken together, our data reveal that the presence of arthropathies in IBD is not accompanied by the presence of different RA serological biomarkers. The differences between positivity in IBD patients with arthropathies and RA patients suggest that the immuno-pathogenesis of arthropathies in IBD may differ from mechanisms in RA patients. More studies are required to investigate these differences. Furthermore, this study implies that there is no apparent clinical value in detecting these RA biomarkers in the serum of IBD patients with arthropathies.

REFERENCES

1. Pincus T, Callahan LF, Sale WG, et al. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum 1984;27:864-72.
2. Landewé RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46(2):347-56.
3. Landewé RBM. The benefits of early treatment in rheumatoid arthritis: confounding by indication, and the issue of timing. Arthritis Rheum 2003;48(1):1-5.
4. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: clinical applications. Dis Markers 2013;35(6):727-34.
5. Kudo-Tanaka E, Ohshima S, Ishii M, et al. Autoantibodies to cyclic citrullinated peptide 2 (CCP2) are superior to other potential diagnostic biomarkers for predicting rheumatoid arthritis in early undifferentiated arthritis. Clin Rheumatol 2007;26:1627-33.
6. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis 2010;69:490-94.
7. Dos Anjos LM, Pereira IA, d'Orsi E, et al. A comparative study of IgG second- and third generation anti-cyclic citrullinated peptide (CCP) ELISAs and their combination with IgA third-generation CCP ELISA for the diagnosis of rheumatoid arthritis. Clin Rheumatol 2009;28(2):153-58.
8. Shi J, Knevel R, Suwannalai P, et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc Natl Acad of Sci USA 2011;108:17372–77.
9. Shi J, van Veelen PA, Mahler M, et al. Carbamylation and antibodies against carbamylated proteins in autoimmunity and other pathologies. Autoimmun Rev 2014;13(3):225-30.
10. Verheul MK, van Erp SJ, van der Woude D, et al. Anti-carbamylated protein antibodies: a specific hallmark for rheumatoid arthritis. Comparison to conditions known for enhanced carbamylation; renal failure, smoking and chronic inflammation. Ann Rheum Dis 2016;75(8):1575-76.
11. Shi J, van de Stadt LA, Levarht EWN, et al. Anti-Carbamylated Protein Antibodies are present in arthralgia patients and predict the development of rheumatoid arthritis. Arthritis & Rheumatism 2013;65:911-15.
12. Gan RW, Trouw LA, Shi J, et al. Anti-carbamylated protein antibodies are present prior to rheumatoid arthritis and are associated with its future diagnosis. J Rheumatol 2015;42(2):572-79.
13. Ryu Jung H, Takeuchi F, Kuwata S, et al. The diagnostic utilities of anti-agalactosyl IgG antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factors in rheumatoid arthritis. Rheumatol Int 2011;31:315-19.
14. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860-65.
15. Van Erp SJ, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. Journal of Crohns and Colitis 2016;10(2):166-75.
16. Brophy S, Pavy S, Lewis P, et al. Inflammatory eye, skin, and bowel disease in spondyloarthritis: genetic, phenotypic, and environmental factors. J Rheumatol 2001;28(12):2667-73.

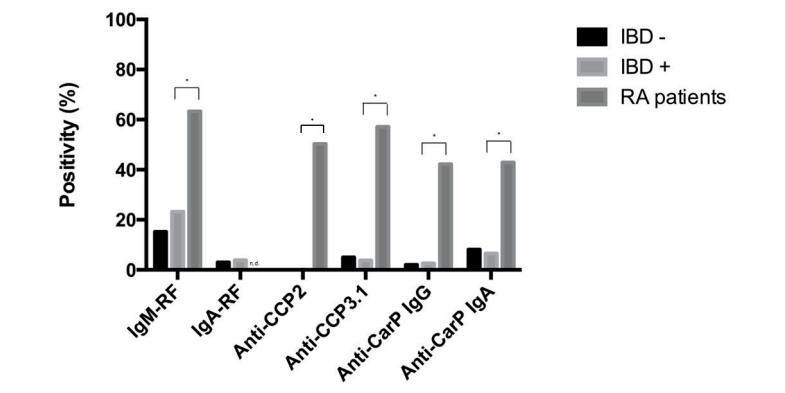
17. Raychaudhuri S, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J. Autoimmun 2014;48-49:128-33.
18. Van Aken J, van Bilsen JH, Allaart CF, et al. The Leiden Early Arthritis Clinic. Clin Exp Rheumatol 2003;21(5 Suppl 31):S100-5.
19. Linn-Rasker SP, van der Helm-van Mil AHM, van Gaalen FA, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. Ann Rheum Dis 2006;65:366-71.
20. Krol A, Garred P, Heegaard NH, et al. Interactions between smoking, increased serum levels of anti-CCP antibodies, rheumatoid factors, and erosive joint disease in patients with early, untreated arthritis. Scan J Rheumatol 2015;44(1):8-12.
21. Bogliolo L, Alpini C, Caporali R, et al. Antibodies to cyclic citrullinated peptides in psoriatic arthritis. J Rheumatol 2005;32(3):511-15.
22. Haga HJ, Palm Ø, Peen E. Prevalence of IgA class antibodies to cyclic citrullinated peptide in patients with inflammatory bowel disease (IBD). Clin Rheumatol 2011;30:955-57.
23. Papamichael K, Tsirogianni A, Papasteriades C, et al. Low prevalence of antibodies to cyclic citrullinated peptide in patients with inflammatory bowel disease regardless of the presence of arthritis. Eur J Gastroenterol Hepatol 2010;22(6):705-9.
24. Koutroubakis IE, Karmiris K, Bourikas L, et al. Antibodies against cyclic citrullinated peptide (CCP) in inflammatory bowel disease patients with or without arthritic manifestations. Inflamm Bowel Dis 2007;13:504-5.
25. Mikuls TR, Hughes LB, Westfall AO, et al. Cigarette smoking, disease severity and autoantibody expression in African Americans with recent-onset rheumatoid arthritis. Ann Rheum Dis 2008;67(11):1529-34.

TABLES AND FIGURES

Table 1. Characteristics of the IBD patients (n=254).

	IBD patients with arthropathies (n=155)	IBD patients without arthropathies (n=99)	P-value
Type of IBD, n (%)			0.04
Crohn's Disease	121 (78.1)	66 (66.7)	
Ulcerative Colitis	34 (21.9)	33 (33.3)	
Male, n (%)	46 (29.7)	50 (50.5)	0.001
Age at inclusion (years), mean ± SD	43.4 ± 13.6	42.7 ± 13.6	0.70
Age of IBD onset (years), mean ± SD	27.5 ± 11.3	25.9 ± 10.1	0.26
IBD disease duration (years), mean ± SD	15.4 ± 11.8	16.3 ± 11.1	0.54
Smoker, n (%)	47 (30.0)	13 (13.1)	0.001
Positive IgM-RF, n (%)	36 (23.2)	15 (15.2)	0.12
Positive IgA-RF, n (%)	6 (3.9)	3 (3.0)	0.73
Positive anti-CCP2, n (%)	0 (0.0)	0 (0.0)	-
Positive anti-CCP3.1, n (%)	6 (3.8)	5 (5.0)	0.71
Positive anti-CarP IgG, n (%)	4 (2.6)	2 (2.0)	0.77
Positive anti-CarP IgA, n (%)	10 (6.5)	8 (8.1)	0.62

Figure 1. Differences in biomarker positivity between IBD and RA patients.



Comparisons of the positivity's of IgA-RF, anti-CCP2, IgM-RF, anti-CCP3.1, anti-CarP IgG and anti-CarP IgA in IBD patients with arthropathies (IBD +), IBD patients without arthropathies (IBD -) and RA patients. IgA-RF is not determined (n.d.) in the RA patients.
* p<0.001

CHAPTER 5

Illness perceptions and outcomes in patients with inflammatory bowel disease: Is coping a mediator?

S.J.H. van Erp*, L.K.M.P. Brakenhoff*, M. Vollmann, D. van der Heijde, R.A. Veenendaal, H.H. Fidder, D.W. Hommes, A.A. Kaptein, A.E. van der Meulen-de Jong, M. Scharloo

International Journal of Behavioral Medicine, 2016
** Shared first authorship*

ABSTRACT

Background: Patients with inflammatory bowel disease (IBD) often experience severe impairment in different life domains. Psychological factors, such as illness perceptions and coping, may play a role in the adjustment to IBD as indicated by mental and physical health, activity and work impairment. The present study aimed at examining the assumption of the Common Sense Model (CSM) that coping mediates the relationship between illness perceptions and adjustment in patients with IBD.

Methods: In a cross-sectional design, 211 IBD patients (73% Crohn's disease, 40% male, mean age 42.9±12.9 years) attending an outpatient clinic completed questionnaires assessing illness perceptions (IPQ-R), coping (CORS), mental and physical health (SF-36) as well as activity and work impairment (WPAI). Multiple mediation analyses were applied that allow estimating the total and direct effects of all illness perception dimensions and the indirect effects through all coping strategies on the illness outcomes simultaneously.

Results: The analyses yielded significant direct effects of perceptions regarding the cyclical course, the chronic course, the severity of the consequences, the comprehensibility, and the emotional impact of IBD on study outcomes. Additionally, significant indirect effects were found for the perceptions regarding the severity of the consequences, the possibility of personal control, and the comprehensibility of IBD on mental and physical health as well as activity impairment through the use of one specific coping strategy, i.e., reduction of activity.

Conclusion: The results provide evidence for the assumptions of the CSM and suggest the importance of addressing illness perceptions and activity stimulation in quality health care for IBD patients.

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing and remitting disease of the gastrointestinal tract. The clinical course of IBD may be unpredictable and complicated, not only because of intestinal symptoms, but also because of the presence of extra-intestinal manifestations. Joint complaints are the most common extra-intestinal manifestations in patients with IBD and cause significant morbidity.[1-2] The debilitating symptoms and complications of IBD often affect the patients' physical, mental and social well-being, resulting in an impaired quality of life (QoL) compared to the general population.[3] The diagnosis of IBD can be stressful and often causes psychological problems, such as feelings of hostility, despair, denial, sadness, grief and anxiety,[4-5] which can induce long-term psychosocial impairments and negatively affect overall QoL.[6-7] Furthermore, the uncertainty of the disease course makes it challenging for patients to make decisions regarding their work and daily activities, which may result in unemployment or social isolation.[6,8-9] Although work disability has been generally related to the severity of IBD, the contribution of psychological factors remains unclear.[10]

The Common Sense Model (CSM)[11] of self-regulation of health and illness is a useful framework to understand how psychological factors, i.e., illness perceptions and coping, influence illness outcomes in IBD patients.[3,12-17] The CSM proposes that patients develop their own ideas about their illness, i.e., illness perceptions, in order to understand the health threat. Illness perceptions embrace five core dimensions, namely 1) ideas about the identity of the illness consisting of the label as well as the symptoms that are associated with the illness, 2) ideas about the causes of the illness, 3) ideas about the consequences that the illness create, 4) ideas about to what extent the illness can be controlled or cured by own behavior or medical treatment, and 5) ideas about the course of the illness and the duration of the symptoms.[11] Two additional dimensions refer to 6) the emotional impact caused by the illness and 7) the overall comprehensibility of the illness.[18] The CSM proposes further that illness representations determine how patients will cope with their illness, and therefore which cognitive and behavioral strategies they will use in order to deal with their illness. Many different coping strategies depending on the illness have been identified, such as turning to religion, ignoring the illness, seeking social support, withdrawal from activities, venting emotions, wishful thinking, distraction, acceptance, and positive reinterpretation.[19-20] According to the CSM, the used

coping strategies have an effect on the adjustment to an illness as indicated, for example, by psychological, physical, and social well-being. In summary, the CSM maintains that illness perceptions influence adjustment to the illness by triggering the use of certain coping strategies.

Studies using the CSM in patients with IBD have shown that illness perceptions significantly accounted for 11% to 21% of the variance in QoL.[3,12,21-23] Patients who believed their illness would last a short time displayed high QoL scores, while patients who believed their IBD resulted in severe consequences were more likely to have lower QoL scores, thus indicating the contradictory effect of different illness perceptions on patients' QoL.[21] Van der Have et al. found associations between illness perceptions and work disability and activity impairment in IBD patients with joint and/or back pain. Patients who believe in serious consequences and with a perception of weak personal control avoid situations in which they could experience limitations, resulting in more work disability and more activity impairment.[22-24]

Also, previous research showed that illness perceptions influence coping behavior of IBD patients. Patients with IBD, who perceive their illness as understandable and controllable, display more active coping (e.g. problem-focused coping).[12]

Furthermore, coping has been found to be associated with QoL, daily activity and work impairment in patients with IBD.[22,25] In a cross-sectional study, Parekh et al. demonstrated that confrontational, evasive and optimistic coping strategies are the most widely adopted and the most effective ones among patients with IBD.[5] QoL was significantly higher for those patients who primarily used these adaptive coping strategies compared to patients who used maladaptive coping strategies including substance use, behavioral disengagement, self-blame, denial, venting emotions and self-distraction.[5,25] In addition, van der Have et al. showed that coping behavior influences illness outcomes, with the maladaptive coping strategy 'reduction of physical activity' being significantly associated with a reduced QoL and more daily activity impairment.[22]

The present study

The purpose of the present study was to investigate the assumption of the CSM that coping mediates the relationship between illness perceptions and adjustment. Adjustment is conceptualized here as mental and physical health as well

as activity and work impairment in patients with IBD. Complex multiple mediation analyses that allow estimating the total and direct associations of all illness perception dimensions and the indirect associations through all coping strategies on adjustment simultaneously were used. Based on previous research, we hypothesized that negative illness perceptions (e.g., severe consequences and strong emotional representations) would be associated with a reduced mental and physical health as well as more activity and work impairment. Additionally, we expected to find that coping mediates the effects of illness perceptions on the outcomes. Compared to other studies that have investigated the mediation hypothesis of the CSM with separate mediation analyses for each illness perception dimension and/or coping strategy in patients with IBD,[22] the present analyses better reflect the proposed theoretical model.

METHODS

Patient population and data collection

Between July 2009 and February 2010, 255 IBD patients attending the IBD outpatient clinic of the Leiden University Medical Center (LUMC), the Netherlands, were requested to take part in our study. No exclusion or inclusion criteria were specified. The participants had to complete web-based or postal questionnaires assessing demographic characteristics, disease activity, peripheral joint pain, back pain, illness perceptions about IBD, coping strategies, mental and physical health as well as activity and work impairment.[22,26] Of the 255 patients, 245 completed all questionnaires. Finally, the data of the 211 patients who completed the Revised Illness Perception Questionnaire (IPQ-R) regarding their IBD complaints were analyzed. The remaining 34 IBD patients who completed the IPQ-R regarding other diseases, were excluded. The study was approved by the medical ethical committee of the LUMC and all patients signed informed consent.

Measures

Disease activity

In patients with Crohn's disease the Harvey Bradshaw Index (HBI) was used to measure clinical disease activity.[27] The HBI used for the present study consisted of in total 11 items, including general well-being, abdominal pain, daily number of liquid stools and extra-intestinal manifestations (arthralgia, uveitis, erythema nodosum, apthous ulcers, pyoderma gangrenosum, anal fissure, new

fistula and abscess). This web-based questionnaire was completed at home and therefore the question about abdominal mass was excluded.

In patients with Ulcerative Colitis the disease activity was measured by using the Simple Clinical Colitis Activity Index (SCCAI)[28] consisting of 9 items; bowel frequency (during the day), bowel frequency (at night), urgency of defecation, blood in stool, general well-being and extra colonic features (arthritis, uveitis, pyoderma gangrenosum and erythema nodosum). In both the HBI and SCCAI, a score above 4 reflects active disease.

Peripheral joint and/or back pain

At study inclusion, participants were asked 1) whether they currently have painful and/or swollen peripheral joints and 2) whether they currently have back pain that already lasts for 3 months or longer. If one of these questions was answered with yes, it was coded that peripheral joint pain and/or back pain was present.[26]

Illness perceptions

Illness perceptions about IBD were assessed with the revised version of the Illness Perception Questionnaire (IPQ-R), a widely-used questionnaire that has been validated in different patient samples.[18] The IPQ-R contains three parts. The first part measures illness identity and includes 15 common symptoms that patients can attribute to their IBD (yes=1 or no=0), with a summary score ranging from 0 to 15. A higher score represents a stronger belief that the symptoms are part of the IBD.

The second part contains 7 subscales measuring chronic timeline (perceived duration of IBD, 6 items), cyclical timeline (perceived variability in the symptoms of IBD, 3 items), consequences (perceived impact of IBD on patients' life, 6 items), personal control (perceived effectiveness of controlling IBD by own behavior, 6 items), treatment control (perceived effectiveness of controlling IBD by treatment, 5 items), coherence (extent of understanding IBD, 4 items), and emotional representations (perceived emotional impact of IBD, 6 items). Items were answered on a five-point Likert scale ranging from 1 'strongly disagree' to 5 'strongly agree'. For each subscale, mean scores were computed after recoding inversely formulated items. Higher scores reflect stronger beliefs on that particular subscale. Internal reliability of the subscales was relatively high with Cronbach's alphas ranging from 0.78 (cyclical timeline) to 0.88 (emotional

representations). For treatment control, however, Cronbach's alpha was 0.59, indicating that in this patient group beliefs about controlling IBD, improving IBD, and curing IBD do not form a homogeneous scale.

The third part, questions about causal attributions, used the same 5-point scale and consisted of 17 items representing perceived causes of IBD. As the underlying dimensions of perceived causes may vary between diseases, Moss-Morris et al., suggested to perform a principal components analysis (PCA) with VARIMAX-rotation on the causal items.[18] The PCA of causal items produced 4 factors accounting for 59% of the total variance. Items with a factor loading higher than 0.50 were interpreted to represent a particular factor. The first factor accounted for 31% of the variance and included 10 items (stress, own behavior, mental attitude, family problems, working too hard, emotional state, getting older, alcohol use, smoking and personality) and was labelled stress and (stress) behavior. Cronbach's alpha of this factor was 0.90. The second (3 items: virus, diet, bad luck) and third (3 items: poor medical treatment, environment, injury) factor both accounted for 10% of the variance but demonstrated insufficient internal reliability (Cronbach's alphas <0.50) and were therefore excluded from further analyses. The fourth factor accounted for 7% of the variance, consisted of only one item (heredity) and was also excluded from further analyses. The items of the first factor were averaged and a higher score indicates stronger beliefs in stress and (stress) behavior causing the illness.

Coping strategies

Coping strategies were assessed with the Coping with Rheumatic Stressors Questionnaire (CORS).[19] This questionnaire was used because most of the IBD patients in this cohort were diagnosed with joint complaints. The CORS measures eight strategies of coping with pain, with limitations and with dependence, which are the most important stressors in inflammatory rheumatic diseases. Coping strategies related to pain included comforting cognitions (i.e., positive self-instructions, 9 items), decreasing activity (i.e., reduce activity and take more rests, 8 items) and diverting attention (doing or thinking of nice things instead of focusing on the pain, 8 items). Three scales refer to limitations, namely optimism (i.e., positive thinking, 5 items), pacing (i.e., lowering the number and intensity of activities, 10 items) and creative solution seeking (i.e., thinking of new ways to get things done, 8 items). Coping styles related to dependence included acceptation (i.e., take the dependence for granted) and consideration (i.e., trying to be useful to others). Items were answered on a 4-point scale from

1 'seldom or never' to 4 'very often'. Mean scores were calculated with higher scores indicating more frequent use of that particular coping strategy. Internal reliability within the subscales was high (Cronbach's alpha ranging from 0.79 to 0.85).

Quality of life

The Short Form (SF)-36 is a generic questionnaire that measures eight general health concepts, which are grouped within a mental (MCS) and a physical (PCS) component summary score that represent mental health and physical health.[29] MCS consist of the concepts vitality, social function, role limitations due to personal or emotional problems and mental health. Physical functioning, role limitations due to physical health problems, bodily pain and general health perception are included in the PCS. The score for subdomains range from 0 to 100, with higher scores representing better mental and physical health, respectively.[29]

Activity and work impairment

Two items of the Work Productivity and Activity Impairment Questionnaire (WPAI) were used to measure activity impairment and work impairment during the past 7 days.[30] The WPAI has been validated in a number of diseases including IBD.[31] Patients were asked to indicate on 11-point scale ranging from 0 'not at all' to 10 'completely' how much their IBD affected 1) their ability to do their regular daily activities and 2) their productivity while working. The last question was only answered by employed patients. Scores were multiplied with 100 in order to compute percentages from 0 to 100, with a higher percentage indicating greater impairment.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics Version 22.
In a first step, bivariate associations between the study variables were analyzed by means of Pearson correlation analyses. This procedure allows comparing our results with findings of previous studies that reported Pearson correlation coefficients by default.

In a second step, four parallel multiple mediation analyses (one for each illness outcome) were calculated with the illness perception dimensions as independent variables, the coping strategies as mediators, and the illness outcome as dependent variable. In order to keep the number of variables to a minimum,

only those illness perception dimensions and coping strategies that were significantly correlated with the illness outcome were included in the respective mediation analysis.[32] As previous research has shown that disease activity and the experience of pain has a strong impact on illness outcomes in patients with IBD, disease activity as well as present back pain and/or peripheral joint pain were entered as control variables in all analyses.[22,25]

The mediation analyses were performed by using the MEDIATE-macro for SPSS that consecutively runs a number of analyses that estimate the total, direct and indirect effects of illness perceptions on the respective illness outcome.[33] The total and direct effects were estimated by means of a stepwise multiple regression analysis in which illness perception dimensions were entered in the first and coping strategies were entered in the second step. Total effects refer to the specific relationships between each illness perception dimension and the respective illness outcome while controlling for the effect of all other illness perceptions dimensions (first step), and direct effects refer to the specific relationships between each illness perception dimension and the respective illness outcome while controlling for all other illness perception dimensions and all coping strategies (second step). The effects of illness perceptions on coping were estimated by calculating multiple regression analyses with all illness perception dimensions as predictors and the respective coping strategy as outcome. The specific indirect effects of the illness perception dimensions on the respective illness outcome through each coping strategy and their significance were determined by means of the new standard method of estimating indirect effects, i.e., bootstrap analyses with 5000 bootstrap samples.[32] As recommended by Hayes, coefficients will be reported in unstandardized form in order to correctly interpret bootstrap confidence intervals and to map the results directly onto the measurement scales.[32]

RESULTS

Sample

The sample consisted of 211 IBD patients with a mean age of 42.9 years (SD=12.9) and a mean disease duration of 15.9 years (SD=11.3). The majority of the participants was diagnosed with CD, was female and had axial and/or peripheral joint complaints. Clinical and demographic characteristics of the study population are shown in Table 1.

Bivariate associations between illness representations, coping strategies and illness outcomes

The results of the correlation analyses are presented in Table 2. Nearly all illness perception dimensions were significantly correlated with outcome measures. More specifically, a strong illness identity, perceptions of a cyclical timeline, of serious consequences, of low personal and of low treatment control as well as low coherence, strong emotional representations, and strong stress and (stress) behavior attributions were associated with lower levels of mental and physical health as well as elevated levels of impairment.

Various coping strategies also showed significant correlations with illness outcomes. More specifically, more frequent use of the coping strategies decreasing activities to cope with pain and pacing to cope with limitations were related to lower physical and mental health and to more activity and work impairment. In addition, lower optimism was related to worse mental health, while the more frequent use of creative solution seeking and showing consideration was related to worse physical health.

Also, various significant correlations were observed between illness perception dimensions and coping strategies. For example, a strong illness identity, more cyclical timeline perceptions, the perception of serious consequences, and low illness coherence were associated with more frequent use of both coping strategies decreasing activity and pacing. Furthermore, the perception of less serious consequences, less strong emotional representations, and the perception of high personal and treatment control were related to more frequent use of optimism. Also, strong illness identity, acute timeline perceptions, the perception of serious consequences, and the perception of high personal control were associated with more creative solution seeking. Finally, more cyclical timeline perceptions and perceptions of high personal control were correlated with more frequent use of showing consideration.

Total, direct, and indirect effects of illness perceptions on illness outcomes (through coping strategies)

Mental health

The mediation analysis with mental health as dependent variable included the illness representation dimensions identity, timeline cyclical, consequences, personal control, treatment control, illness coherence, emotional representations, and stress and (stress) behavior attributions as independent variable.

The coping strategies decreasing activity, optimism, and pacing as mediators, as well as disease activity and present back and/or peripheral joint pain were included as control variables. The results of the analysis are displayed in Table 3 and Figure 1a. The regression analysis revealed significant total and direct effects for illness coherence and emotional representations on mental health, indicating that low illness coherence and strong emotional representations were associated with worse mental health. Furthermore, bootstrap analyses revealed significant indirect effects of consequences (0.63 BCa 95% CI (1.495-0.072)), personal control (0.34 BCa 95% CI (0.999-0.006)), and illness coherence (0.39 BCa 95% CI (0.026-1.043)) on mental health through decreasing activity. Stronger perceptions of serious consequences and of personal control as well as low illness coherence were associated with the more frequent use of decreasing activity, which in turn was related to lower levels of mental health. All variables together explained 35% of the variance in mental health.

Physical health

The mediation analysis with physical health as dependent variable included the illness representation dimensions identity, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representations as independent variables. The coping strategies decreasing activity, pacing, seeking solutions, and showing consideration as mediators, as well as disease activity and present back and/or peripheral joint pain were included as control variables. The results of the analysis are displayed in Table 3 and Figure 1b. The multiple regression analysis revealed significant total and direct effects of consequences, disease activity and present back and/or peripheral joint pain on physical health, indicating that stronger perceptions of serious consequences and more disease activity and pain were associated with lower levels of physical health. Furthermore, bootstrap analyses again revealed significant indirect effects of consequences (0.51 BCa 95% CI (1.297-0.074)), personal control (0.27 BCa 95% CI (0.842-0.011)) and illness coherence (0.31 BCa 95% CI (0.014-1.015)) on physical health through decreasing activity. Stronger perceptions of serious consequences and of personal control as well as low illness coherence were associated with a more frequent use of decreasing activity, which in turn was related to worse physical health. All variables together explained 42% of the variance in physical health.

Activity impairment

The mediation analysis with activity impairment as dependent variable included the illness representation dimensions identity, timeline cyclical, consequences, personal control, treatment control, illness coherence, emotional representations, and stress and (stress) behavior attributions as independent variables. The coping strategies decreasing activity and pacing as mediators, as well as disease activity and present back and/or peripheral joint pain were included as control variables. The results of the analysis are displayed in Table 3 and Figure 1c. The multiple regression analysis revealed significant total and direct effects of consequences and present back and/or peripheral joint pain on activity impairment, indicating that strong perceptions of negative consequences and more pain were related to more activity impairment. Furthermore, bootstrap analyses again revealed significant indirect effects of consequences (2.20 BCa 95% CI (0.633-4.890)) personal control (1.19 BCa 95% CI (0.156-3.020)), and illness coherence (1.36 BCa 95% CI (3.55-0.241)) on activity impairment through decreasing activity. Stronger perceptions of serious consequences and personal control as well as low illness coherence were related to the more frequent use of decreasing activity, which in turn was related to higher levels of activity impairment. All variables together explained 38% of the variance in activity impairment.

Work impairment

The mediation analysis with work impairment as dependent variable included the illness representation dimensions identity, timeline chronic, timeline cyclical, consequences, treatment control, illness coherence, emotional representations, and stress and (stress) behavior attributions as independent variables. The coping strategies decreasing activity and pacing as mediators, as well as disease activity and present back and/or peripheral joint pain were included as control variables. The results of the analysis are displayed in Table 3 and Figure 1d. The multiple regression analysis revealed significant total and direct effects of timeline chronic, consequences and treatment control on work impairment, indicating that more acute timeline perceptions, stronger perceptions of serious consequences and weaker perceptions treatment effectiveness were associated with more work impairment. Bootstrap analyses revealed no significant indirect effects. All variables together explained 25% of the variance in work impairment.

DISCUSSION

The purpose of this cross-sectional study was to examine the assumption of the CSM that coping mediates the relationship between illness perceptions and adjustment in patients with IBD.[11] To our knowledge, this study was the first to apply multiple mediation analyses that allow estimating the total and direct effects of all illness perception dimensions and the indirect effects through all coping strategies on illness outcomes simultaneously.

The findings of the present study indicate that both illness perceptions and coping play a significant role in adjustment to IBD even after controlling for disease activity and peripheral joint and/or back pain. All variables together could explain a meaningful proportion of the variance in the illness outcomes.

In accordance with the CSM and our hypotheses, the effects of illness perceptions on health outcomes were partially mediated by coping.[11] More specifically, perceptions of more serious consequences, stronger personal control and a lack of personal understanding of IBD were associated with a more frequent use of the coping strategy decreasing activity, which, in turn, was associated with lower mental health, lower physical health and more activity impairment. Two aspects of these results are noteworthy: First, within the mediation models decreasing activity was the only coping strategy that showed significant associations with the illness outcomes and served as a mediator between illness perceptions and illness outcomes. Thus, decreasing activity is of special importance in coping with IBD. Earlier studies already provided initial indications on the significance of this coping strategy, however, in our study, the pattern is most pronounced.[12-13,22] Secondly, although the bivariate correlations between personal control and illness outcomes suggest a positive impact, the indirect effect of personal control on mental and physical health as well as activity impairment was negative. In general, in the CSM stronger perceptions of personal control are seen as beneficial for adaptation, but from our results it seems that feelings of personal control are expressed in the maladaptive coping strategy decreasing activities.[17,34] This contradictory finding should be investigated in future research.

Besides the indirect effect via decreasing activity, several illness perceptions dimensions were also directly, i.e., independently from coping, associated with mental health, physical health, and activity impairment. The direction of these

associations is in line with the assumptions of the CSM and our hypothesis based on previous findings.[11-14,16-17,20] Particularly, a lack of understanding IBD and the experience of more negative emotions are related to worse mental health. Perceptions of more severe consequences have an unfavorable effect on physical health and the capability to engage in daily activity.

Interestingly, with regard to work impairment only direct effects of illness representation were found. Perceiving IBD as acute, as causing severe consequences, and as being non-controllable by treatment were linked to more work impairment. The absence of the mediation effect of the coping strategy decreasing activity might be due to the smaller sample size as only employed patients were included.

Limitations

Some limitations need to be acknowledged. First, the study had a cross-sectional design and therefore, the direction of causality in the associations between illness perceptions, coping and outcomes could not be determined. Longitudinal studies are needed to address this issue, since these could examine the dynamic processes of illness perceptions and coping on illness outcomes specified in the CSM.[11] Second, the present findings are exclusively based on self-reported measures that might be subject to several forms of bias. Further studies could profit from including objective measures (i.e., medical assessments). Third, although back and/or joint pain appears often in IBD patients, the CORS questionnaire has not been validated in these patients and coping strategies linked to IBD-specific stressors might have been missed. However, this questionnaire has been validated in patients with rheumatoid arthritis, an inflammatory joint disease.[18] Future studies investigating the influence of coping on illness outcomes in patients with IBD should use an illness-specific coping questionnaire, i.e. the newly developed IBD-Cope.[35]

Conclusions

Despite these limitations, the present study contributes to a better understanding of the interplay between illness perceptions, coping and adjustment to IBD. Illness perceptions and coping were shown in this cross-sectional study to influence quality of life and activity impairment. Adjustment to IBD can be improved, apart from medical interventions, by psychological interventions.[34,36-39] The healthcare team has to anticipate on the patients disease behavior by improving the understanding of IBD and/or modifying illness perceptions and coping

strategies. Briefer questionnaires with easy scoring schemes need to be developed to assess illness perceptions and coping strategies to improve the illness outcomes by psychological interventions too. The newly developed IBD-Cope is in this way an improvement.[35] Previous studies determined that changing illness perceptions and coping strategies is associated with improved outcomes. Chilcot et al. showed in patients with irritable bowel syndrome (IBS) that illness perceptions became more positive following cognitive-behavioral therapy (CBT) compared with usual care. CBT enhanced perceived control, facilitated more coherence, reduced perceptions of severe consequences and predicted improved work and social adjustment.[36] Previous studies in IBD patients found these effects of CBT as well, suggesting that influencing cognitive factors and behavioral aspects could lead to improved functioning in IBD.[36-39] In addition, Petrie et al. designed a program to modify asthma patients' illness perceptions by sending text messages that were created to push an illness perception in a direction more consistent with higher adherence.[39] In IBD patients a text message program might be effective to increase coherent understanding of the disease and to reduce the perception of serious consequences. Based on findings of the current study, behavioral interventions increasing illness coherence, modifying perceptions of the severity of consequences and reducing the use of the maladaptive coping strategy decreasing activity may result in an increase in mental and physical health as well as less activity and work impairment.

For a health professional, it is important to pay attention to the illness perceptions of IBD patients, because they may lead to a low QoL and impairment. Knowledge and understanding of illness perceptions, coping strategies and the effect on illness outcomes can help health professionals to understand the IBD patients' disease behaviors and improve the QoL by supporting the ability to cope with stressors related to disease. Assessing illness perceptions and coping strategies in IBD, therefore, is part and parcel of quality health care.

REFERENCES

1. 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.
2. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860-65.
3. Van der Have M, Minderhoud IM, Kaptein AA, et al. Substantial impact of illness perceptions on quality of life in patients with Crohn's disease. J Crohns Colitis 2012;7:292-301.
4. Fuller-Thomson E, Lateef R, Sulman J. Robust association between inflammatory bowel disease and generalized anxiety disorder: findings from a nationally representative Canadian study. Inflamm Bowel Dis 2015;21(10):2341-48.
5. Parekh NK, McMaster K, Nguyen DL, et al. Coping strategies used by adult patients with inflammatory bowel disease. South Med J 2015;108:337-42.
6. Casati J, Toner BB. Psychosocial aspects of inflammatory bowel disease. Biomed Pharmacother 2000;54:388-93.
7. Casati J, Toner BB, de Rooy EC, et al. Concerns of patients with inflammatory bowel disease. Dig Dis Sci 2000;45:26-31.
8. Bernklev T, Jahnsen J, Henriksen M, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12:402-12.
9. Feagan BG, Bala M, Yan S, et al. Unemployment and disability in patients with moderately to severely active Crohn's disease. J Clin Gastroenterol 2005;39:390-95.
10. Ramos A, Calvet X, Sicilia B, et al. IBD-related work disability in the community: Prevalence, severity and predictive factors. A cross-sectional study. United European Gastroenterol J 2015;3(4):335-42.
11. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In L. D. Cameron & H. Leventhal (Eds.) The self-regulation of health and illness behaviour. London: Routledge; 2003. pp. 42-65.
12. Dorrian A, Dempster M, Adair P. Adjustment to inflammatory bowel disease: the relative influence of illness perceptions and coping. Inflamm Bowel Dis 2009;15:47-55.
13. Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to inflammatory bowel disease. Inflamm Bowel Dis 2010;16:1685-95.
14. Knowles SR, Cook SI, Tribbick D. Relationship between health status, illness perceptions, coping strategies and psychological morbidity: A preliminary study with IBD stoma patients. J Crohns Colitis 2013;7:471-78.
15. Knowles SR, Grass C, Macrae F. Illness perceptions in IBD influence psychological status, sexual health and satisfaction, body image and relational functioning: A preliminary exploration using Structural Equation Modeling. J Crohns Colitis 2013;7:344-50.
16. Knowles SR, Wilson JL, Connell WR, et al. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the Common Sense Model of illness. Inflamm Bowel Dis 2011;17:2551-57.
17. Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. J Health Psychol 2012;18:972-83.
18. Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R).

Psychol Health Med 2002;17:1-16.
19. Van Lankveld W, van 't Pad Bosch P, van de Putte L, et al. Disease-specific stressors in rheumatoid arthritis: coping and well-being. Br J Rheumatol 1994;33:1067-73.
20. Haggar SM, Orbell S. A Meta-Analytic Review of the Common-Sense Model of Illness Representations. Psychology & Health 2003;18(2):141-84.
21. Han SW, McColl E, Barton JR, et al. Predictors of quality of life in ulcerative colitis. The importance of symptoms and illness representations. Inflamm Bowel Dis 2005;11:24-34.
22. 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.
23. Van der Have M, Fidder HH, Leenders M, et al. Self-reported disability in patients with inflammatory bowel disease largely determined by disease activity and illness perceptions. Inflamm Bowel Dis 2015;21:369-77.
24. Netjes JE, Rijken M. Labor participation among IBD patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19(1):81-91.
25. McCombie AM, Mulder RT, Gearry RB. Coping strategies and psychological outcomes of patients with inflammatory bowel disease in the first 6 months after diagnosis. Inflamm Bowel Dis 2015;21(10):2272-80.
26. Van Erp SJH, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2015;9(3):276-83.
27. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1(8173):876.
28. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29–32.
29. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
30. Zhang W, Bansback N, Boonen A, et al. Validity of the work productivity and activity impairment questionnaire – general health version in patients with rheumatoid arthritis. Arthritis Res Ther 2010;12(5):R177.
31. Reilly MC, Gerlier L, Brabant Y, et al. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. Clin Ther 2008;30:393-404.
32. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York: Guilford Press. 2013.
33. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. Br J Math Stat Psychol 2014;67:451-70.
34. Tiggelman D, van de Ven MOM, van Schayck OCP, et al. The Common Sense Model in early adolescents with asthma: Longitudinal relations between illness perceptions, asthma control and emotional problems mediated by coping. J Psychosom Res 2014;77(4):309:15.
35. McCombie A, Swaminathan A, Mulder R, et al. The IBD-Cope: A New Instrument for Measuring Coping in Inflammatory Bowel Disease Patients. J Crohns Colitis 2016;10(6):678-86.
36. Chilcot H, Moss-Morris R. Changes in illness-related cognitions rather than distress mediate improvements in irritable bowel syndrome (IBS) symptoms and disability following a brief cognitive behavioural therapy intervention. Behav Res Ther 2013;51:690-95.
37. Mikocka-Walus A, Bampton P, Hetzel D, et al. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel

disease: a pilot randomized controlled trial. BMC Gastroenterol 2015;15:54.
38. Mussell M, Bocker U, Nagel N, et al. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. Scand J Gasteroenterol 2003;38(7):755-62.
39. Petrie KJ, Perry K, Broadbent E, et al. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. Br J Health Psychol 2012;17:74-84.

TABLES AND FIGURES

Table 1. Clinical and demographic characteristics of the study population (n=211).

Variable	IBD patients (n=211)
Type of IBD, n (%)	
Crohn's Disease	154 (73.0)
Ulcerative Colitis	57 (27.0)
Age (years), mean ± SD	42.9 ± 12.9
Male, n (%)	84 (39.8)
Disease duration (years), mean ± SD	15.9 ± 11.3
Employed, n (%)	137 (64.9)
Montreal Classification	
Location CD, n (%)	*n=154*
L1 ileal	38 (24.7)
L2 colonic	30 (19.5)
L3 ileocolonic	72 (46.8)
L4 upper	1 (0.7)
L1-3+L4	13 (8.4)
Behaviour CD, n (%)	
B1 non-stricturing/penetrating	67 (43.5)
B2 stricturing	22 (14.3)
B3 penetrating	21 (13.6)
+ perianal disease	44 (28.6)
Extension UC, n (%)	*n=57*
E1 ulcerative proctitis	5 (8.8)
E2 left sided UC	17 (29.8)
E3 extensive UC (pancolitis)	35 (61.4)
Medication, n (%)	
Mesalazine	55 (26.1)
Corticosteroids	26 (12.3)
Immunosuppressive drugs (Aza/6MP/MTX)	75 (35.5)
Anti-TNF	74 (35.1)
None	47 (22.3)
Control variables	
Joint and/or back pain	124 (58.8)
Active IBD disease	83 (39.3)

Table 2. Means (M) and standard deviations (SD) of the study variables and intercorrelations between illness perceptions [1 to 9], coping [10 to 17] and illness outcomes.

	10	11	12	13	14	15	16	17	Mental health	Physical health	Activity impairment	Work impairment	M	SD
1.Identity	.01	.30***	.13	-.08	.32***	.20**	.05	.07	-.25***	-.36***	.34***	.22**	4.74	2.84
2. Timeline chronic	-.03	-.05	-.20**	-.08	.02	-.14*	.03	.01	-.10	.04	-.02	-.18*	4.30	0.58
3. Timeline cyclical	.18**	.24***	.12	.02	.15*	.10	.05	.18*	-.18**	-.34***	.31***	.29***	3.60	0.82
4. Consequences	-.04	.41***	.003	-.15*	.37***	.14*	.02	.04	-.41***	-.48***	.49***	.39***	3.06	0.83
5. Personal control	.11	-.01	.17*	.22**	-.003	.21**	.21**	.18**	.21**	.23**	-.19**	-.09	2.93	0.69
6. Treatment control	.07	-.17*	.13	.18**	-.12	.07	-.01	-.03	.17*	.28***	-.29***	-.18*	3.19	0.55
7. Illness coherence	.03	-.23**	.02	.05	-.15*	-.08	.01	-.08	.44***	.19**	-.26***	-.22*	3.73	0.76
8. Emotional representations	-.18*	.21**	-.11	-.29***	.11	.04	-.10	.003	-.54***	-.22**	.32***	.24**	2.61	0.83
9. Stress and behavior attributions	-.04	.11	.10	-.04	.07	.08	.00	.05	-.20**	-.07	.16*	.21**	2.24	0.75
10. Comforting cognitions	-	-	-	-	-	-	-	-	.01	-.13	.02	.06	-	-
11. Decreasing activity	-	-	-	-	-	-	-	-	-.29***	-.39***	.41***	.30***	-	-
12. Diverting attention	-	-	-	-	-	-	-	-	-.03	-.12	.01	.06	-	-
13. Optimism	-	-	-	-	-	-	-	-	.16*	.03	-.08	-.09	-	-
14. Pacing	-	-	-	-	-	-	-	-	-.16*	-.38***	.34***	.19**	-	-
15. Solution seeking	-	-	-	-	-	-	-	-	-.10	-.17*	.10	.09	-	-
16. Accepting dependence	-	-	-	-	-	-	-	-	.07	.000	-.01	-.04	-	-
17.Showing consideration	-	-	-	-	-	-	-	-	-.10	-.16*	.05	.08	-	-
M	2.89	2.24	2.36	2.93	2.33	2.48	2.13	2.70	46.74	46.99	36.07	23.14	-	-
SD	0.55	0.53	0.57	0.60	0.56	0.54	0.62	0.52	9.75	9.56	29.26	29.02	-	-

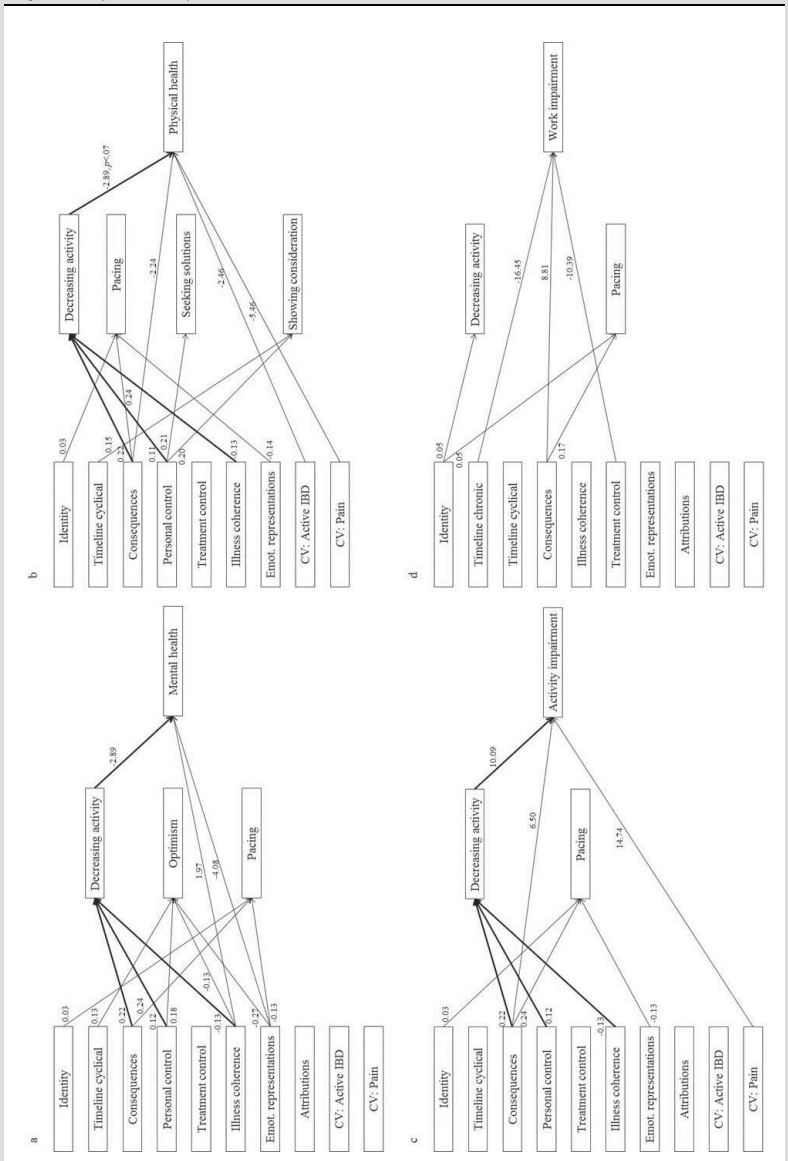
*** p < .001, ** p < .01, * p < .05.

Table 3. Total and direct effects of illness perception dimensions and direct effects of coping strategies on illness outcomes.

	Mental health		Physical health		Activity impairment		Work impairment	
	B step 1	B step 2	B step 1	B step 2	B step 1	B step 2	B step 1	B step 2
Step 1:	adj. R^2 = .34, F(10, 200) = 11.93***		adj. R^2 = .39, F(9, 201) = 15.99***		adj. R^2 = .35, F(10, 200) = 12.50***		adj. R^2 = .25, F(10, 126) = 5.59***	
Identity	-0.12	-0.09	-0.31	-0.21	0.76	0.47	1.11	0.85
Timeline chronic	-	-	-	-	-	-	-17.23**	-16.45**
Timeline cyclical	0.70	0.88	-1.77*	-1.38	3.30	2.46	2.93	2.60
Consequences	-1.37	-0.97	-3.16**	-2.24*	9.29**	6.50*	9.43**	8.81*
Personal control	1.08	1.30	0.77	1.35	-0.49	-1.90	-	-
Treatment control	0.00	-0.22	1.12	0.75	-5.05	-4.26	-10.57*	-10.38*
Illness coherence	2.23*	1.97*	0.84	0.25	-3.33	-1.70	0.71	0.65
Emotional representations	-4.01***	-4.08***	1.51	0.98	-0.23	0.97	1.23	1.09
Stress and (stress) behavior attributions	-0.51	-0.52	-	-	2.08	2.25	1.31	0.99
Control variable: active IBD	-2.10	-1.99	-2.54**	-2.46**	6.03	5.67	5.90	5.66
Control variable: pain	-0.98	-1.07	-5.78***	-5.46***	15.04***	14.74***	5.15	5.29
Step 2:	adj. R^2 = .35, F(13, 197) = 9.62***		adj. R^2 = .42, F(13, 197) = 12.60***		adj. R^2 = .38, F(12, 198) = 11.91***		adj. R^2 = .25, F(12, 124) = 4.79***	
Decreasing activity	-	-2.89*	-	-2.35	-	10.09*	-	6.62
Optimism	-	0.17	-	-	-	-	-	-
Pacing	-	0.95	-	-2.01	-	2.20	-	-1.24
Solution seeking	-	-	-	0.67	-	-	-	-
Showing consideration	-	-	-	-1.38	-	-	-	-

An empty cell means that the respective illness perception dimension/coping strategy was not included in the analysis. Unstandardized coefficients are reported. B's of step 1 represent total effects and B's step 2 represent direct effects. *** p < .001, ** p < .01, * p < .05.

Figure 1. Results of the four mediation analyses. Only paths that are significant at $p < .05$ are displayed, unless stated otherwise. Unstandardized coefficients are reported. Significant indirect effects are indicated by bold printed paths. CV = control variable.



CHAPTER 6

The impact of arthropathies on illness perceptions, coping strategies, outcomes and their changes over time in IBD patients: a 12-month follow-up study

S.J.H. van Erp*, M. van der Have*, H.H. Fidder, D. van der Heijde, R. Wolterbeek, D.W. Hommes, A.A. Kaptein, A.E. van der Meulen-de Jong

European Journal of Gastroenterology and Hepatology, 2018
** Shared first authorship*

ABSTRACT

Background: Arthropathies are a common extra-intestinal manifestation (EIM) in inflammatory bowel disease (IBD). This study evaluated the differences in illness perceptions, coping strategies and illness outcomes between IBD patients with and without arthropathies at baseline, and examined changes at 12 months in these variables in patients with arthropathies.

Methods: In total, 204 patients with (n=123) and without (n=81) arthropathies completed questionnaires at baseline and after 1 year assessing illness perceptions, coping, quality of life (QoL) and work and activity impairment. A linear regression analysis assessed the impact of arthropathies on these factors compared to patients without arthropathies. A mixed model analysis evaluated changes in illness perceptions, coping and outcomes in patients with arthropathies over time.

Results: Patients with arthropathies had more persistent thoughts on symptomatology and the variability of symptoms, held more negative views on the effects of illness, had heightened emotions that impacted daily functioning and had a poorer understanding of IBD than patients without arthropathies. Patients with arthropathies could more efficiently divert attention, felt more useful to others and perceived a reduced physical and mental health and an increased activity impairment compared with patients without arthropathies. At follow-up, patients with arthropathies were more sceptical about the effectiveness of medical treatment, but were better able to adapt their activities to their complaints compared with baseline.

Conclusion: Patients with arthropathies in IBD adopt different illness perceptions, coping strategies and outcomes compared with patients without arthropathies, which is important to know when designing behavioural and physical interventions to improve functioning.

INTRODUCTION

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC) are immune-mediated chronic inflammatory diseases of the gastrointestinal tract characterized by periods of inflammation and remission. Receiving a diagnosis of IBD can be stressful, and can impact illness outcomes such as quality of life (QoL), activity impairment and work productivity in a variety of ways.[1-4] IBD is associated with a range of extra-intestinal manifestations (EIMs) of which arthropathies, with a prevalence of approximately 30%, are the most common.[5-7] Arthropathies can be subdivided into inflammatory (spondyloarthritis; SpA) and non-inflammatory (arthralgia) musculoskeletal symptoms. Recent studies have shown the significant impact of arthritis and IBD separately on different illness outcomes. It is well recognized that disability in patients with arthritis and in patients with IBD is not only associated with clinical variables of the disease process itself, but also with behavioural factors including illness perceptions and coping strategies.[8-10] Illness perceptions are individual cognitions and emotions about a disease.[11] Coping refers to cognitive and behavioural efforts and strategies to deal with stressful stimuli, such as a chronic illness. Different coping styles may be required to deal with the various aspects of a disease.[12] Understanding and targeting the illness perceptions and coping strategies of IBD patients with and without arthropathies by medical or psychological interventions may improve treatment in this patient population and may thereby improve illness outcomes including QoL, and activity and work impairment.

We have shown that arthropathies in IBD patients have a strong negative impact on QoL and work impairment.[13] However, it is unknown whether this is caused by differences in illness perceptions, coping strategies and illness outcomes in IBD patients with and without arthropathies. Therefore, our goal in the present study was to examine the differences in illness perceptions, coping strategies and illness outcomes between IBD patients with and without arthropathies. A secondary aim of our study was to evaluate changes in illness perceptions, coping strategies and outcomes at 12 months follow-up in IBD patients with arthropathies. This line of research might be instrumental in identifying targets for intervention via addressing and changing maladaptive illness perceptions and coping styles.

METHODS

Our cohort was based on the JOINT cohort[5], which includes 255 IBD patients (155 with and 100 without self-reported arthropathies), all with a long IBD disease duration.[14] Of these 255 patients, 204 were included in the present study based on completion of all questionnaires at study inclusion and after 1-year follow-up. Of the 204 participants, 178 patients completed the questionnaires based on their IBD, of which 109 had self-reported joint complaints. Subsequently, 8 patients fulfilled the questionnaires based on having arthropathies and 18 patients completed the questionnaires regarding other diseases. IBD patients were classified with self-reported arthropathies when they had chronic back pain (CBP) and/or peripheral joint complaints currently or during the previous year. A rheumatologic examination was performed in all 204 patients (123 patients with and 81 without self-reported joint complaints) at baseline and after 12-months follow-up. At both study time points patients were asked to complete questionnaires about disease activity, illness perceptions, coping strategies, quality of life, as well as activity and work impairment.[11,15-19] Illness perceptions were measured with the Revised Illness Perception Questionnaire (IPQ-R). This questionnaire covers 8 subscales including 'Identity' (thoughts about the illness and the symptoms associated with it), 'Timeline chronic' (cognitions about the duration), 'Timeline cyclical' (perceived variability of symptoms), 'Consequences' (ideas about the severity of the illness and the impact on daily functioning), 'Personal control' (cognitions about the manageability of the illness through personal efforts), 'Treatment control' (perceptions about the effectiveness of medical treatment), 'Emotional representations' (the emotional impact) and 'Illness coherence' (personal understanding of the illness).[13] Coping strategies were evaluated with the Coping with Rheumatic Stressors Questionnaire (CORS), which assesses eight coping strategies covering the different consequences of coping with pain, limitations and dependence.[17] Coping strategies covering pain included 'Comforting cognitions' (self-encouragement), 'Decreasing activity' (taking more rest) and 'Diverting attention' (thinking about nice things). Strategies covering limitations encompassed 'Optimism' (thinking positively), 'Pacing' (adapting the level of activities) and 'Creative solution seeking' (creative things to achieve a goal). Strategies related to dependence included 'Acceptance' (making an effort to accept one's dependence) and 'Consideration' (being useful to others). Illness outcomes included QoL, activity and work impairment. QoL was measured with the Short Form (SF)-36 and was subdivided into physical health via the physical component score (PCS) and mental

health by the mental component score (MCS).[18] Activity and work impairment was measured with the Work Productivity Activity Index (WPAI).[19] The study was approved by the institutional medical ethical committee of the LUMC and patients signed a written informed consent prior to study enrolment.

Statistics

All analyses were performed in SPSS, version 23.0. Descriptive statistics were used for patients' characteristics, and comparisons of the baseline characteristics of patients with and without arthropathies were analysed with an independent t-test and a chi-square test. Linear regression models were used to assess potential associations of arthropathies as a predictor of illness perceptions, coping strategies and outcomes in IBD patients. Variables with a statistical level of $p \leq 0.05$ in the univariate analysis were included in the multivariate analysis. The multivariate analysis included 'arthropathies' as the independent variable, adjusted for age, gender, IBD disease activity, smoking, employment status and 5-ASA treatment, since these variables were significantly different at baseline between study groups. For the follow-up analysis, a linear mixed model was used. IBD patients with arthropathies at baseline were included in this analysis and compared with the follow-up sample consisting of the same IBD patients with arthropathies except for the patients who reported a cessation of their joint complaints after 1-year. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Demographic data

Of the 204 IBD patients included in the present study, 123 (60.3%) had self-reported arthropathies and 81 (39.7%) had no arthropathies. IBD patients with arthropathies had a mean IBD disease duration of 15.3 (SD=12.0) years at study inclusion, a mean age of 44.1 (SD=13.8) years, and were representative of the JOINT cohort.[5] IBD patients with arthropathies were more often diagnosed with Crohn's Disease (CD) ($p=0.03$), an active disease course ($p < 0.001$), with a mean Harvey Bradshaw Index (HBI) of 6.0 ($p<0.001$) and were more often smokers ($p=0.009$) compared with IBD patients without arthropathies. Of the 123 patients with arthropathies, 63 patients (51.2%) reported peripheral joint complaints only, 12 patients (9.8%) reported back pain and 48 (39%) reported both axial and peripheral joint complaints. In total, 13 (10.6%) patients were formally

diagnosed with arthritis by a rheumatologist based on physical examination and radiographs. Sixteen patients (13%) met the ASAS criteria for axial and peripheral SpA. IBD patients without arthropathies (n=81) were more likely to be male (p=0.003), employed (p=0.007) and were more often treated with 5-ASA (including sulfasalazine or mesalazine) for their IBD (p=0.02) compared with the patients with arthropathies (Table 1). Of the 123 IBD patients with self-reported arthropathies at baseline, 12 reported a cessation of joint complaints at 1-year follow-up, leaving a total of 111 (90.2%) patients with joint complaints. In the group without arthropathies (n=81), 4 of 81 patients developed self-reported arthropathies during the 12-months follow-up.

Differences in illness perceptions, coping strategies and outcomes between IBD patients with and without arthropathies at baseline

Univariate analyses showed that arthropathies in IBD patients were associated with the illness perceptions 'identity' ß (95% CI): 1.05 (0.73 to 2.28), p<0.001; 'cyclical timeline' 1.63 (0.70 to 2.55), p=0.001; 'consequences' 2.52 (1.17 to 3.86), p=0.001, 'personal control' -1.22 (-2.34 to -0.11), p=0.032, 'emotional representations' 1.69 (0.31 to 3.06), p=0.017, 'illness coherence' -1.36 (-2.42 to -0.31), p=0.011 and 'treatment control' -0.83 (-1.58 to -0.07), p=0.031. In addition, arthropathies were associated with the coping strategies 'decreasing activity' 1.33 (0.15 to 2.51), p=0.027, 'diverting attention' 1.61 (0.39 to 2.82), p=0.010, 'pacing' 1.72 (0.16 to 3.29), p=0.031 and 'consideration' 1.11 (0.11 to 2.11), p=0.030). Significant associations between arthropathies and the following illness outcomes were found: 'physical health' -3.61 (-6.25 to -0.97), p=0.008, 'mental health' -9.00 (-11.40 to -6.12), p<0.001, 'activity' 0.21 (0.14 to 0.29), p<0.001 and 'work impairment' 0.11 (0.01 to 0.20), p=0.030.

In the multivariate model, arthropathies remained associated with a strong 'identity' 1.15 (0.31 to 1.98), p=0.007, more 'cyclical timeline' 1.33 (0.33 to 2.34), p=0.010, increased 'consequences' 2.00 (0.60 to 3.42), p=0.006, more 'emotional representations' 1.58 (0.08 to 3.08), p=0.039 and less 'illness coherence' -1.29 (-2.45 to -0.14), p=0.029 compared with patients without arthropathies. These results indicate that IBD patients with arthropathies had more persistent thoughts about symptoms and the perceived variability of these symptoms associated with illness, they had more negative beliefs about the effect of IBD, they experienced an increased emotional burden of the illness on daily life and had a reduced coherence of IBD compared with patients without arthropathies (Table 2). Furthermore, arthropathies in IBD were related to increased 'diverting

attention' 1.34 (0.02 to 2.66), p=0.047, more 'consideration' 1.18 (0.10 to 2.27), p=0.033. The illness outcomes including a poorer 'mental health' -3.10 (-5.99 to -0.23), p=0.035 and 'physical health' -7.22 (-9.68 to -4.77), p<0.001, and elevated levels of 'activity impairment' 0.15 (0.07 to 0.23), p<0.001 were found in IBD patients with arthropathies. More specifically, IBD patients with arthropathies were better able to alter the focus of their attention, were more helpful to others, but experienced poor physical and mental health, and greater activity impairment compared to IBD patients without arthropathies.

Follow-up

The secondary aim of the present study was to examine changes of illness perceptions and coping strategies in IBD patients with arthropathies at 1-year follow-up. After 12 months, IBD patients with arthropathies had lower scores on the illness perception dimension 'treatment control' (p=0.001), but had an increased score on the coping strategy 'pacing' (p=0.030) (Table 3). These results indicate that IBD patients with arthropathies perceived the use of medical interventions having little efficacy, but they were more able to adapt the level and intensity of their activities in daily life over time.

DISCUSSION

In this longitudinal follow-up study, we explored the effect of IBD-related arthropathies on illness perceptions, coping strategies and outcomes, and evaluated the changes in these factors at 1-year follow-up in IBD patients with arthropathies. The findings of this study indicate that persistent thoughts on symptomatology, perceived variability of symptoms, increased negative ideas regarding illness, increased emotional impact on daily functioning and less personal understanding of IBD, were all illness perceptions more commonly perceived by patients with arthropathies compared to patients without arthropathies.

In the present study, we found a different coping pattern in patients with arthropathies compared to patients without arthropathies. IBD patients with arthropathies were more able to divert attention and were trying to be more useful to others. Parekh et al. have reported that patients who use optimistic, adaptive coping styles have an increased QoL compared to IBD patients who use evasive coping styles.[20] In contrast to the report by Parekh et al., patients

with arthropathies in the present study applied these optimistic coping strategies ('diverting attention' and 'consideration') more frequently, but still reported a reduced mental and physical health and elevated levels of activity impairment compared with patients without arthropathies. This impaird QoL in IBD patients with arthropathies, subdivided into mental and physical health, has also been found in a study with patients with psoriatic arthritis (PsA) compared with patients with psoriasis only (PsO). Patients with PsA experienced greater physical disability than those with PsO, reflecting the functional disability due to the musculoskeletal disease. As a contrast with our results, no differences were found regarding mental health between the PsA and PsO patients.[21]

In the present study, IBD patients with arthropathies had less faith in the effectiveness of medical treatment at 1-year follow-up. This may be attributed to the fact that patients still reported arthropathies after one year, despite regular medical IBD treatment, indicating that this medical intervention was ineffective in alleviating their joint complaints. Furthermore, we have previously reported that active IBD is associated with arthropathies.[5] In this study, the mean HBI and Simple Clinical Colitis Activity Index (SCCAI) showed a score above 4, signifying active IBD.

Bijsterbosch et al. studied changes in illness perceptions over a period of 6 years in patients with osteoarthritis (OA). Over this period, understanding of the illness (i.e., 'illness coherence') increased, patients perceived their illness as less manageable and more chronic, but associated fewer negative emotions with the OA. Patients who displayed increased symptoms, a negative impact on daily life and had stronger beliefs regarding chronicity after 6 years follow-up experienced a progression of disability.[9] IBD patients with arthropathies were better able to adapt the number and intensity of activities to their complaints after 1 year follow-up, indicating that they adjusted to IBD-related symptoms compared to baseline. In patients with RA and diabetes mellitus (DM), Gåfvels et al. described a change in coping strategies during 24 months follow-up. In both patient groups, less perceived effort was required to reduce the problems associated with disability and less support was obtained from family and friends. In addition, RA patients perceived a reduced ability to adapt to disease-related disability.[22]

Some limitations need to be acknowledged. A first limitation of our study was cohort selection. We included IBD patients with a mean disease duration of

15.3 years and a mean arthropathy duration of 11.6 years after IBD diagnosis. Broadbent et al. reported that most illness perceptions are created in the first months after the patient is diagnosed with a disease.[23] In addition, once an illness perception has been developed, this perception will hardly change over time.[24] Future studies should include newly diagnosed IBD patients ideally with concurrent or future onset of arthropathies. The second limitation that needs to be mentioned is that 178 of the 204 IBD patients completed the questionnaires regarding their IBD, of which 109 patients had self-reported joint complaints. Only 8 completed the questionnaires based on arthropathies. Nevertheless, the apparent differences in illness perceptions, coping and outcomes between the groups with and without arthropathies found in the present study probably indicate that IBD patients with arthropathies consider IBD and arthropathies to be one disease and thus attribute subconsciously one illness perception, coping strategy or outcome to both diseases. A third limitation is that the CORS questionnaire used in the present study was originally designed to measure coping in RA patients and has not been validated in IBD patients. Though, this questionnaire was considered appropriate in the present study since the CORS has been validated in patients with RA, an inflammatory joint disease. Future research could use the recently developed IBD-Cope to evaluate the coping strategies in IBD patients and this could be compared with results obtained by the CORS.[25]

Despite these limitations, the present study provides a better understanding of the impact of arthropathies on illness perceptions, coping and outcomes in IBD patients. However, although arthropathies in IBD were associated with different illness perceptions, coping strategies and outcomes compared to patients without arthropathies, for the health professional it is important that these issues are addressed for all IBD patients visiting the outpatient clinic. It is also important that the gastroenterologist actively listens to a patient's complaints and additionally explores the impact of the disease on daily functioning. This may modify the maladaptive illness perceptions; the perceived diversity of symptoms related to IBD, strong (negative) views concerning severity, the increased emotional impact and the lower coherence of the illness in IBD patients. Furthermore, the gastroenterologist should be aware of the impact of IBD-associated arthropathies on mental and physical health and activity impairment. Effects that might possibly be reduced by physical exercise and psychosocial interventions.[26-27] Cognitive behavioural therapy (CBT) or mindfulness-based therapies appear to be effective in IBD patients, resulting in

improved QoL, medical therapy adherence and coping, and should therefore be considered in the health management of these patients.[28]

Although, over the long-term, IBD patients with arthropathies became more sceptical about the efficacy of medical interventions, they were better able to adapt physical activity to their complaints compared to patients without arthropathies. Knowledge and understanding of these progressive changes in patients' illness perceptions and coping strategies should help stimulate the promotion, for recently diagnosed patients with IBD and arthropathies, of CBT and face-to-face consultations with a psychologist aimed at disease self-management. Furthermore, it is important that gastroenterologists provide a clear explanation of the intended effects of medication on arthropathies and the importance of achieving IBD remission, since disease activity is associated with arthropathy.[5]

REFERENCES

1. Alarhayem A, Achebe E, Logue AJ. Psychosocial support of the inflammatory bowel disease patient. Surg Clin North Am 2015;95:1281–93.
2. Regueiro M, Greer JB, Szigethy E. Etiology and treatment of pain and psychosocial issues in patients with inflammatory bowel disease. Gastroenterol 2017;152:430-39.
3. Bernklev T, Jahnsen J, Henriksen M, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12:402-12.
4. Feagan BG, Bala M, Yan S, et al. Unemployment and disability in patients with moderately to severely active Crohn's disease. J Clin Gastroenterol 2005;39:390-95.
5. Van Erp SJH, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2016;10:166–75.
6. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860-65.
7. 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.
8. Mattila K, Buttgereit F, Tuominen R. Impact of morning stiffness on working behaviour and performance in people with rheumatoid arthritis. Rheumatol Int 2014;34:1751–58.
9. Bijsterbosch J, Scharloo M, Visser AW, et al. Illness perceptions in patients with osteoarthritis: Change over time and association with disability. Arthr Rheum 2009;61(8):1054-61.
10. Dorrian A, Dempster M, Adair P. Adjustment to inflammatory bowel disease: the relative influence of illness perceptions and coping. Inflamm Bowel Dis 2009;15:47-55.
11. Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R). Psychol Health 2002;17:1-16.
12. Aldwin CM, Brustrom J. Theories of coping with chronic stress. In: Gottlieb BH, ed. Coping with Chronic Stress. New York, NY: Plenum Press; 1997:75–103.
13. Van Erp SJH, Brakenhoff LKMP, Vollmann M, et al. Illness perceptions and outcomes in patients with inflammatory bowel disease: Is coping a mediator? Int J Behav Med 2017;24:205–14.
14. 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(3):276-83.
15. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1(8173):876.
16. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29–32.
17. Van Lankveld W, van 't Pad Bosch P, van de Putte L, et al. Disease-specific stressors in rheumatoid arthritis: coping and well-being. Br J Rheumatol 1994;33:1067-73.
18. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
19. Zhang W, Bansback N, Boonen A, et al. Validity of the work productivity and activity impairment questionnaire – general health version in patients with rheumatoid arthritis. Arthritis Res Ther 2010;12(5):R177.

20. Parekh NK, McMaster K, Nguyen DL, et al. Coping strategies used by adult patients with inflammatory bowel disease. South Med J 2015;108:337-42.
21. Rosen CF, Mussani F, Chandran V, et al. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatol 2012;51(3):571–76.
22. Gåfvels C, Hägerström M, Rane K, et al. Coping strategies among patients newly diagnosed with diabetes or rheumatoid arthritis at baseline and after 24 months. J Health Psychol 2016.
23. Broadbent E, Wilkes C, Koschwanez H, et al. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. Psychol Health 2015;30(11):1361-85.
24. Fischer M, Scharloo M, Abbink J, et al. The dynamics of illness perceptions: Testing assumptions of Leventhal's common-sense model in a pulmonary rehabilitation setting. Br J Health Psychol 2010 Nov;15(Pt 4):887-903.
25. McCombie A, Swaminathan A, Mulder R, et al. The IBD-Cope: A New Instrument for Measuring Coping in Inflammatory Bowel Disease Patients. J Crohns Colitis 2016;10(6):678-86.
26. Lykouras D, Karkoulias K, Triantos C. Physical exercise in patients with inflammatory bowel disease. J Crohns Colitis 2017;11(8):1024.
27. Mussell M, Bocker U, Nagel N, et al. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. Scand J Gasteroenterol 2003;38(7):755-62.
28. Ballou S, Keefer L. Psychological interventions for irritable bowel syndrome and inflammatory bowel diseases. Clin Transl Gastroenterol 2017;8(1):e214.

TABLES

Table 1. Baseline characteristics.

	IBD patients with arthro-pathies (n=123)	IBD patients without arthropathies (n=81)	P-value
Type of IBD, n (%)			0.03
Crohn's disease	95 (77.2)	51 (63.0)	
Ulcerative colitis	28 (22.8)	30 (37.0)	
Male, n (%)	40 (32.5)	43 (53.1)	0.003
Age at inclusion (years), mean (SD)	44.1 (13.8)	44.5 (13.7)	
Age of IBD onset (years), mean (SD)	28.4 (11.9)	26.6 (10.4)	
IBD disease duration (years), mean (SD)	15.3 (12.0)	17.4 (11.6)	
HBI, mean (SD)	6.0 (4.9) (n=95)	2.3 (2.5) (n=51)	<0.001
SCCAI, mean (SD)	4.1 (1.6) (n=28)	3.6 (2.0) (n=30)	0.49
Smoker, n (%)	36 (29.3)	11 (13.6)	0.009
Employed, n (%)	68 (55.3)	60 (74.1)	0.007
Current medication use, n (%)			
5-ASA (mesa, sulfa)	20 (16.3)	24 (29.6)	0.02
Steroids	8 (6.5)	2 (2.5)	0.19
Immunosuppressive drugs (Aza/6MP/MTX)	28 (22.8)	17 (21.0)	0.78
Anti-TNF	33 (26.8)	23 (28.4)	0.81
None	34 (27.6)	15 (18.5)	0.14
Type of joint complaints, n (%)			
Peripheral joint complaints	63 (51.2)	-	
Back pain	12 (9.8)	-	
Both	48 (39.0)	-	
Diagnosed with arthritis and fulfilled the ASAS criteria*, n (%)	13 (10.6%)	-	

*ASAS criteria for SpA
HBI = Harvey Bradshaw Index, SCCAI = Simple Clinical Colitis Activity Index, SD = Standard Deviation.

Table 2. Univariate and multivariate linear regression models showing potential associations for arthropathies as a predictor for illness perceptions, coping strategies and illness outcomes in IBD (n=204; 123 patients with self-reported arthropathies).

	Univariate		Multivariate*	
Variable	**Beta (95% CI)**	**P-value**	**Beta (95% CI)**	**P-value**
Demographic characteristics				
Type of IBD	0.14 (0.02 to 0.27)	0.027		
CD (ref)				
UC				
Gender				
Male (ref)	0.21 (0.07 to 0.34)	0.003		
Female				
Active IBD				
Yes (ref)	0.26 (0.13 to 0.40)	<0.001		
No				
Smoking				
Yes (ref)	0.16 (0.04 to 0.27)	0.009		
No				
Employed				
Yes (ref)	-0.18 (-0.32 to -0.05)	0.006		
No				
5-ASA treatment	-0.13 (-0.25 to -0.02)	0.023		
Yes (ref)				
No				
Illness perceptions				
Identity	1.05 (0.73 to 2.28)	<0.001	1.15 (0.31 to 1.98)	0.007
Timeline chronic	0.17 (-0.78 to 1.12)	0.729	-	-
Timeline cyclical	1.63 (0.70 to 2.55)	0.001	1.33 (0.33 to 2.34)	0.010
Consequences	2.52 (1.17 to 3.86)	0.001	2.00 (0.60 to 3.42)	0.006
Personal control	-1.22 (-2.34 to -0.11)	0.032	-0.83 (-2.03 to 0.37)	0.176
Emotional representations	1.69 (0.31 to 3.06)	0.017	1.58 (0.08 to 3.08)	0.039
Illness coherence	-1.36 (-2.42 to -0.31)	0.011	-1.29 (-2.45 to -0.14)	0.029
Treatment control	-0.83 (-1.58 to -0.07)	0.031	-0.48 (-1.28 to 0.31)	0.230
Coping strategies				
Comforting cognitions	1.36 (-0.04 to 2.76)	0.057	-	-
Decreasing activity	1.33 (0.15 to 2.51)	0.027	0.64 (-0.61 to 1.88)	0.316
Diverting attention	1.61 (0.39 to 2.82)	0.010	1.34 (0.02 to 2.66)	0.047
Optimism	0.58 (-0.29 to 1.44)	0.190	-	-
Pacing	1.72 (0.16 to 3.29)	0.031	0.87 (-0.73 to 2.46)	0.286
Creative solution seeking	1.0 (-0.14 to 2.14)	0.086	-	-
Acceptation	0.24 (-0.86 to 1.33)	0.670	-	-
Consideration	1.11 (0.11 to 2.11)	0.030	1.18 (0.10 to 2.27)	0.033
Illness outcomes				
Mental health	-3.61 (-6.25 to -0.97)	0.008	-3.10 (-5.99 to -0.23)	0.035
Physical health	-9.00 (-11.40 to -6.12)	<0.001	-7.22 (-9.68 to -4.77)	<0.001
Activity impairment	0.21 (0.14 to 0.29)	<0.001	0.15 (0.07 to 0.23)	<0.001
Work impairment	0.11 (0.01 to 0.20)	0.030	0.09 (-0.02 to 0.20)	0.094

*Beta's shown in the multivariate model represent the value for the variable 'arthropathies' adjusted for demographic characteristics (type of IBD, gender, active IBD, smoking, employment status and 5-ASA).

Table 3. Changes in illness perceptions, coping strategies and illness outcomes in IBD patients with arthropathies in 1-year follow-up.

	IBD patients with arthropathies t = 0 (n=123)	IBD patients with arthropathies t = 12 (n=111)	P-value*
Illness perceptions, mean (SD)			
Identity	4.95 (2.83)	4.97 (2.87)	0.95
Timeline chronic	26.08 (3.39)	26.12 (2.73)	0.92
Timeline cyclical	14.68 (2.91)	14.79 (2.66)	0.67
Consequences	19.50 (4.40)	19.79 (4.64)	0.34
Personal control	17.00 (3.77)	17.11 (3.96)	0.72
Emotional representations	16.08 (5.02)	15.58 (5.36)	0.18
Illness coherence	18.15 (3.97)	18.43 (3.89)	0.45
Treatment control	15.53 (2.83)	14.56 (3.05)	0.001
Coping, mean (SD)			
Comforting cognitions	26.63 (4.49)	26.45 (4.37)	0.64
Decreasing activity	18.41 (3.77)	18.70 (4.26)	0.35
Diverting attention	19.36 (3.99)	19.30 (4.10)	0.89
Optimism	14.94 (3.09)	14.86 (3.13)	0.78
Pacing	24.13 (5.37)	25.16 (5.49)	0.03
Creative solution	20.31 (3.96)	20.66 (4.46)	0.42
Accepting	12.82 (3.86)	13.15 (3.65)	0.35
Consideration	19.38 (3.48)	19.54 (3.11)	0.61
Illness outcomes, mean (SD)			
PCS	43.42 (9.00)	43.76 (9.28)	0.63
MCS	45.33 (10.16)	45.36 (10.16)	0.98
Work impairment (n)	0.29 (0.29) *(n=68)*	0.27 (0.27) *(n=62)*	0.78
Activity impairment	0.43 (0.27)	0.40 (0.28)	0.26

SD = Standard Deviation. *Mixed model analysis.

CHAPTER 7

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

M. van der Have*, L.K.P.M. Brakenhoff*, S.J.H. van Erp, A.A. Kaptein, M. Leenders, M. Scharloo, R.A. Veenendaal, D. van der Heijde, A.E. van der Meulen-de Jong, D.W. Hommes, H.H. Fidder

Journal of Crohn's and Colitis, 2016
** Shared first authorschip*

ABSTRACT

Background: Back and joint pain are the most common extra-intestinal symptoms reported by patients with inflammatory bowel disease (IBD). We assessed the impact of back/joint pain, illness perceptions, and coping on quality of life (QoL) and work productivity in patients with IBD.

Methods: Our cohort included 155 IBD patients with and 100 without arthropathy. Arthropathy was defined as daily back pain for ≥ 3 months and/or peripheral joint pain and/or joint swelling over the last year. At baseline and at 12 months, patients completed questionnaires on the extent of back/joint pain, IBD disease activity, illness perceptions, coping, QOL, and work productivity. The impact of back/joint pain, illness perceptions and coping on QOL and work productivity was determined, using linear mixed models.

Results: In total, 204 IBD patients (72% Crohn's disease, 40% male, mean age 44±14 years) completed questionnaires at both time points. At both time points, IBD patients with back/joint pain reported a significantly lower QoL and work productivity compared with IBD patients without back/joint pain. Predictors of low QoL were back/joint pain (ß −1.04, 95% confidence interval (CI) −1.40 to −0.68), stronger beliefs about the illness consequences (ß −0.39, 95%CI: −0.59 to −0.18) and emotional impact of IBD (ß −0.47, 95%CI: −0.66 to −0.28), and the coping strategy 'decreasing activity' (ß −0.26, 95%CI: −0.48 to −0.03). Predictors of work productivity were back/joint pain (ß 0.22, 95%CI: 0.07 to 0.37) and illness consequences (ß 0.14, 95%CI: 0.06 to 0.22).

Conclusion: Back/joint pain, illness perceptions, and coping are significant predictors of QOL and work productivity, after controlling for disease activity.

INTRODUCTION

Arthropathies are the most common extra-intestinal manifestations (EIMs) in patients with inflammatory bowel disease (IBD), with prevalence rates ranging between 1 and 46%.[1-10] In general, arthropathies affect young IBD patients at the peak of their working life and are therefore potentially associated with high morbidity and increased costs.[11] IBD-associated arthropathy is considered a subtype of spondylarthropathy and may involve both peripheral and axial joints. Back and joint pain (hereafter referred to as 'back/joint pain') are the most important clinical manifestations of IBD-associated arthropathy.

Although back/joint pain is major problem in the general population,[12] data on the impact of back/joint pain on the quality of life (QoL) and work disability in patients with IBD are scarce. According to a population-based study[3] and a cross-sectional study,[4] QoL was significantly reduced in IBD patients with non-inflammatory joint pain and self-reported arthritis, respectively. Yet the impact of back/joint pain on work productivity and the relationships between back/joint pain, illness perceptions, coping, and important outcomes such as QoL and work productivity has not been assessed before.[3-4]

It has been shown clearly that QoL and other health outcomes are associated not only with the disease itself, but also with factors such as illness perceptions and coping. The relationships between disease characteristics, illness perceptions, coping, and health outcome are supported by the Common Sense Model.[13-14] According to this model, patients generate both cognitive and emotional representations (known as illness perceptions) in response to a perceived health threat or illness. Illness perceptions provide a framework for patients to make sense of their symptoms and create a coherent view of their illness. This in turn guides coping strategies, such as decreasing or pacing activities, with potential impact on health outcomes such as QoL and work productivity. Thus, the impact of illness perceptions on health outcomes may be attenuated by adopting a certain coping strategy.

The efficacy and validity of the Common Sense Model has been shown in patients with various chronic illnesses, such as rheumatoid arthritis and multiple sclerosis.[15-16] Previous studies in IBD have also found strong relationships between illness perceptions, coping, and various health outcomes, including QoL, psychological distress (depression and anxiety), sexual health, and disa-

bility.[17-25] Improving our understanding of the relationships between back/joint pain, illness perceptions, and coping behaviors in patients with IBD may provide possible targets for biopsychosocial interventions aimed at reducing morbidity and costs and increasing patients' QoL.

In this prospective study we aimed to examine the impact of back/joint pain, illness perceptions, and coping on QoL and work productivity in a carefully selected group of IBD patients, after controlling for demographic and clinical characteristics.

MATERIAL & METHODS

Patient population and study design

Between July 2009 and February 2010, 258 IBD patients were systematically assessed by a multidisciplinary team of gastroenterologists and rheumatologists at the JOINT outpatient clinic of the Leiden University Medical Centre. The systematic assessment consisted of a medical history (extra-intestinal manifestations, medication use), physical examination (distribution of painful joints, enthesitis, dactylitis)[26], laboratory tests (C-reactive protein, erythrocyte sedimentation rate, HLA-B27), and signs of sacroiliitis on X-ray (optional).[27] Based on this assessment 155 (60.1%) patients with and 100 (38.8%) patients without arthropathy were identified. Arthropathy was defined as chronic back pain for at least 3 months, and/or peripheral joint pain/swelling at presentation or during the previous year. Three patients (1.1%) with fibromyalgia were excluded.

Patients were then prospectively followed for 12 months. At baseline and at 12 months of follow-up, patients completed a web-based or postal questionnaire covering demographic characteristics (age, gender, and working status), the presence and extent of back/joint pain, illness perceptions, coping strategies, QoL, work productivity, and activity impairment (see below). Variables concerning IBD subtype and the Montréal classification were obtained from medical records.

As we were primarily interested in the impact of current back/joint paint on QoL and work productivity, the patient population was divided into patients with and without back/joint pain as reported at baseline. Obviously, as we relied on self-reported data, the presence of joint swelling could not be ascertained.The

study was centrally approved by the Ethics Committee of the Leiden University Medical Center. All patients an signed informed consent form.

Predictors

Back/joint pain and IBD clinical disease activity

Back/joint pain was quantified using two 11-point numeric rating scales, one for back pain and one for joint pain, ranging from 0 ('no back/joint pain') to 10 ('worst imaginable back/joint pain') during the previous week. The mean score was used for patients reporting both back and joint pain. Clinical IBD activity was measured with the well-validated Harvey Bradshaw Index (10 items, excluding the question about abdominal mass)[28] and the Simple Clinical Colitis Activity Index (nine items)[20] for patients with Crohn's disease (CD) and ulcerative colitis (UC), respectively. A score > 4 indicated active disease.

Illness perceptions

Illness perceptions were measured with the Revised Illness Perception Questionnaire (IPQ-R).[30] For the present study, eight subscales of the IPQ-R were used: 'Illness identity' (number of symptoms that patients associate with IBD); 'Timeline chronic' (expected duration of IBD); 'Timeline cyclical' (expected cyclical symptomatology of IBD); 'Consequences' (negative consequences for the patients' lives); 'Personal control' (perceived personal control over IBD); 'Treatment control' (perceived efficacy of treatment); 'Emotional representations' (negative emotions resulting from IBD); and 'Coherence' (personal understanding of IBD). The Illness identity subscale is calculated by summing the symptoms (range 0–14) that patients associate with IBD. For the other subscales items are rated on a five-point Likert scale (from 'strongly disagree' to 'strongly agree'). To facilitate interpretation of these subscales, mean scores are presented. Subscales showed a high internal reliability (Cronbach's α ranging from 0.76 to 0.89), except for the 'Treatment control' subscale (0.59), which was therefore excluded from further analysis.

Coping

Coping was measured with the Coping with Rheumatic Stressors questionnaire (CORS), covering eight coping strategies directed at the most important stressors of immune-mediated inflammatory disease (e.g. IBD), including pain, limitations, and dependency.[31] Coping strategies directed at pain included 'Comforting cognitions' (self-encouragement, putting the pain into perspective; nine items), 'Decreasing activities' (eight items), and 'Diverting attention'

(thinking about something nice; eight items). Coping strategies directed at limitations included 'Optimism' (five items), 'Pacing' (adapting one's level of activity; 10 items), and 'Creative solution seeking' (finding creative solutions to cope with limitations in work, household activities, leisure time, and hobbies; eight items). Coping strategies directed at dependency included 'Accepting' (making an effort to accept one's level of dependency; six items) and 'Consideration' (thoughtful concern for others; seven items). For each item, patients reported how often they employed a particular coping strategy (1 = 'seldom or never', 2 = 'sometimes', 3 = 'often', 4 = 'very often'). Higher scores indicate more frequent use of a particular coping strategy. Internal reliability within the subscales was high (Cronbach's α ranging from 0.78 to 0.86).

Health outcomes: QoL, work productivity and activity impairment

The QoL was measured with both a disease-specific and a generic questionnaire. The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was developed as a short version of the IBDQ, and is a simple, validated 10-item questionnaire that assesses disease-specific QoL of patients with IBD.[32-33] Total scores range from 10 to 70, with a higher score indicating better QoL. The Short-Form 36 (SF-36) is a generic questionnaire comprising 36 items, grouped within a Physical Component Score (PCS) and a Mental Component Score (MCS).[34] The PCS consist of physical functioning, role of limitations due to physical health problems, bodily pain, and general health perception. The MCS consists of vitality, social function, role limitations due to personal or emotional problems, and mental health. Each component score has a score ranging from 0 to 100, with a high score indicating better functional status.

The Work Productivity and Activity Impairment questionnaire (WPAI) assesses the impact of IBD on work productivity and daily activities during the previous 7 days.[35-36] It generates four component scores: percentage of work time missed (absenteeism); percentage of impairment while working (presenteeism); percentage of overall work impairment (absenteeism and presenteeism combined); and percentage of activity impairment. Unemployed patients only answered questions relating to employment status and activity impairment. Scores for WPAI range from 0 ('no impairment') to 100 ('total loss of work productivity/activity or work impairment').

Statistics

Data analyses were performed using SPSS 20.0 and SAS 9.2. Descriptive statistics were used to characterize CD and UC patients. Means and medians were reported with a standard deviation (SD) and interquartile range (IQR), respectively. Mean baseline differences with regard to QoL, work productivity, and activity impairment between patients with and without back/joint pain were determined using the paired Student's t-test. Univariate analyses were performed to assess associations between back/joint pain, illness perceptions, coping, and outcomes, including QoL, work productivity, and activity impairment. To correct for multiple testing, the level of significance was set at $p<0.007$ (0.05/7) and $p<0.006$ (0.05/8) for the illness perceptions (seven IPQ-R subscales) and coping (eight CORS subscales), respectively. Linear mixed models with random intercept were used to assess the independent effects of back/joint pain, illness perceptions, and coping on QoL, work productivity, and activity impairment. Independent variables that reached significance in univariate analyses were included. Based on previous data,[37] gender and disease activity were included as covariates. To assess whether back/joint pain, illness perceptions, and coping contributed to the variance of outcomes, multiple linear mixed models were used. With the Common Sense Model as the theoretical framework, back/joint pain was entered in the first step, illness perceptions in the second step, and coping strategies in the third step. The likelihood ratio test (difference of −2 log likelihood between two steps) was performed to assess whether each step significantly improved our model.

RESULTS

Baseline characteristics of study population

The baseline questionnaire was completed by 245/255 patients (response rate 96.1%), of whom 204 also completed the follow-up questionnaire at 12 months (loss to follow-up 16.7%) (Figure 1). Thus, the 204 patients who completed questionnaires at both time points constituted our study population. Of the 204 patients, 146 (71.6%) had CD and 58 (28.4%) had UC, with a mean age of 44.3 (SD=13.7) years and a median disease duration of 15.0 (IQR 7.0–24.0) years (Table 1). In CD, ileocolonic disease (65/146; 44.5%), and inflammatory behavior (62/146; 42.5%) were the most common disease phenotypes. In UC, pancolitis (34/58; 58.6%) was the dominant disease phenotype. Based on the numeric rating scale, back/joint pain was present in 113/204 (55.4%) patients,

of whom 41 (36.3%) had peripheral joint pain, 8 (7.1%) had back pain, and 64 (56.6%) had mixed complaints. At physical examination, 45/105 (42.9%) patients with peripheral or mixed joint complaints had four or more tender joints (polyarticular). Enthesitis was present in 2 (1.0%) patients, dactylitis in 2 (1.0%), and extra-intestinal manifestations in 49 (24.0%) patients. Further investigations revealed an elevated C-reactive protein in 30 (14.7%) patients, elevated erythrocyte sedimentation rate in 42 (20.9%), HLA-B27 seropositivity in 7/118 (5.9%), and sacroiliitis on X-ray in 5/123 (4.1%) patients.

Supplementary Material A (page 196) shows data on baseline demographic and clinical variables in completers and non-completers. There were no relevant statistical significant differences between both groups, except that non-completers had a significantly younger mean age (38.4 versus 44.3 years, p=0.011).

Baseline levels of quality of life, work and activity impairment

IBD patients with back/joint pain had significantly lower levels of disease-specific QoL (SIBDQ: 47.8±10.7 vs. 55.1±8.7) and generic QoL (SF-36 PCS: 41.9±8.9 vs. 52.1±7.6; SF-36 MCS: 45.1±10 vs. 48.7±8.6) at baseline as compared to IBD patients without back/joint pain (Figure 2). Additionally, IBD patients with back/joint pain had significantly higher levels of work impairment (45.0±9.9 vs. 22.0±3.3) and activity impairment (37.0±8.1 vs. 19.0±2.9) at baseline as compared to IBD patients without back/joint pain (Figure 2).

Predictors of QoL and work activity impairment

Based on the univariate analyses (Supplementary Material B (page 197)), each of the illness perceptions and coping strategies were significantly associated with QoL, work and activity impairment and, therefore, were included in multiple linear mixed models. Clinical disease activity was significantly associated with back/joint pain (ß 2.04, p<0.0001), with a variance inflation factor of 1.00, indicating no multicollinearity.

In the first step of our multivariate model we assessed whether back/joint pain was associated with disease-specific QoL (SIBDQ), generic QoL (SF-36 PCS and SF-36 MCS), work impairment, and activity impairment (Tables 2-4), while controlling for gender and IBD activity. Back/joint pain was significantly associated with SIBDQ ß (95%CI): -1.04 (-1.40 to -0.68), SF-36 PCS -1.69 (-2.00 to -1.38), SF-36 MCS -0.48 (-0.87 to -0.10), work impairment 0.22 (0.07 to 0.37), and activity impairment 0.48 (0.39 to 0.58).

In the second step of our multivariate model we assessed whether the addition of illness perceptions significantly improved our first model, using the likelihood ratio test (difference in -2 Log Likelihood between both models). The addition of illness perceptions improved the first model for all health outcomes (p=0.01). 'Illness consequences' were significantly associated with SIBDQ ß (95%CI): -0.39 (-0.59 to -0.18), SF-36 PCS -0.59 (-0.77 to -0.40), work impairment 0.14 (0.06 to 0.22) and activity impairment 0.13 (0.07 to 0.18), meaning that low QoL and work and activity impairments were associated with stronger beliefs that IBD will have negative consequences for the person's life. 'Emotional representations' were significantly associated with SIBDQ ß (95%CI): -0.47 (-0.66 to -0.28), SF-36 MCS -0.72 (-0.93 to -0.52), and activity impairment 0.06 (0.01 to 0.12), meaning that low QoL and a high activity impairment were associated with negative beliefs about how the illness affects one's emotional well-being.

In our third model we assessed whether the addition of coping significantly improved our second model. The addition of coping improved the second model across SF-36 PCS (p=0.00), SF-36 MCS (p=0.00), and activity impairment (p=0.00). 'Decreasing activity' was significantly associated with SIBDQ ß (95%CI): -0.26 (-0.48 to -0.03), SF-36 PCS -0.21 (-0.41 to -0.01), SF-36 MCS -0.42 (-0.66 to -0.18), and activity impairment 0.10 (0.04 to 0.17). In addition, we assessed whether the impact of illness perceptions on health outcomes was mediated by particular coping strategies. 'Decreasing activity' mediated the impact of the illness perceptions 'identity' and 'consequences' on both SF-36 PCS and SF-36 MCS.

DISCUSSION

In this prospective study of patients with IBD-associated arthropathy, we found that back/joint pain had a negative impact on QoL and work productivity. This negative impact on QoL and work productivity remained significant during a follow-up of 12 months, after controlling for gender and IBD activity. Additionally, the QoL and work productivity of IBD patients were also highly determined by several illness perceptions and, to a lesser extent, by coping.

To our knowledge, this is the first study to date assessing the impact of illness perceptions and coping on QoL and work productivity in patients with IBD-associated arthropathy.

Although QoL and work productivity were mainly determined by back/joint pain and activity of IBD, illness perceptions contributed significantly to the variance of these outcomes. Our findings are in line with previous studies in CD and UC assessing the impact of disease characteristics and illness perceptions on various health outcomes.[17-18,23] In these studies, disease characteristics (mainly disease activity) contributed 49–68%[20-21,26] and 23%[17] of the variance of QoL and disability, respectively. Illness perceptions contributed an additional 9–21%[17-18,23] and 23%[17] of variance of QoL and disability, respectively. In this study we have demonstrated that a decrease in QoL was highly associated with stronger beliefs that IBD will have negative consequences for one's life (i.e. illness consequences), and negative beliefs about how IBD affects one's emotional well-being (i.e. emotional representations). The strong impact of illness consequences and emotional representations has been confirmed by previous studies in IBD. For instance, in a study of 80 IBD patients it was shown that illness consequences were moderately or strongly associated with different aspects of adjustment to their disease, including psychological distress, QoL and functional independence.[17]

We also examined whether coping added significantly to the variance of health outcomes, after controlling for gender, disease activity, and remaining illness perceptions. Coping is defined as ongoing cognitive or behavioral efforts to manage psychological distress.[38-39] Coping strategies (or styles) can either be active (problem-based) or passive (emotion-based). Active coping (creative solution seeking, decreasing activities, and pacing) aims to alter or eliminate the source of stress, while passive coping (consideration, accepting, optimism) aims to reduce the emotional distress caused by the situation. Patients with IBD are more likely to rely on passive coping strategies.[40-42] Consistent with previous evidence in IBD, we found that coping significantly added to the variance of QoL and impairments in daily activity.[24-25] However, other studies in IBD did not observe a contributory role of coping with respect to QoL, psychological distress and functional independence.[17,23] This may be explained by the fact that in these studies coping was assessed with a generic coping questionnaire, which tends to obscure associations between illness-specific coping, QoL, and activity and work impairments. In the present study we used the disease-specific coping questionnaire, which addresses coping strategies directed at the most important stressors of immune-mediated inflammatory diseases, including pain, limitations, and dependency.

Additionally, we found that the behavioral coping strategy 'decreasing activities' was negatively associated with QoL and activity impairments. This association has not been observed in IBD before. In patients with rheumatoid arthritis and ankylosing spondylitis, decreasing activity has been clearly found to be negatively associated with QoL,[43] functional status,[44-45] and work productivity.[46] It has been postulated that avoidance (i.e. decreasing activities) may have beneficial effects in the short term by facilitating healing in rheumatoid arthritis. However, in the long term it becomes a maladaptive coping strategy by limiting joint movement and inducing muscle weakness and disuse.[47-49]

Finally, we have demonstrated that the impact of illness perceptions, in particular illness identity and illness consequences, on QoL is reduced when patients do not decrease activity in order to cope with pain. This mediating effect supports the Common Sense Model,[13-14] which states that the impact of illness perceptions on health outcomes may be attenuated by adopting a particular coping strategy.

This study has several important strengths. First, all patients were systematically examined by a multidisciplinary team of gastroenterologists and rheumatologists. Second, patients were prospectively followed for 12 months, which enabled us to assess the predictive value of back/joint pain, illness perceptions, and coping on several important patient-reported health outcomes. Third, the results of our multiple linear mixed models strongly support the well-validated Common Sense Model. This study has also several limitations. First, as reflected by the relatively high proportion of anti-tumor necrosis factor users, our study included a selected patient group. Therefore, extrapolation of our data to the general IBD population may be limited. However, the primary aim of the present study was to determine associations between back/joint pain, illness perceptions, and coping that are also applicable to population-based samples. Second, attrition bias may have occurred due to differences between patients who did and did not complete the follow-up period. However, demographic and disease characteristics were similar between the two groups, except for the lower age of the non-completers. We consider that this difference did not affect our outcomes, since age was not found to be associated with QoL and work productivity (Supplementary Material B). Third, as the CORS has not been validated in patients with IBD-associated arthropathy, coping strategies directed at IBD-specific stressors such as abdominal pain, urgency, and diarrhoea might have been missed. However, the CORS has been extensively validated in patients with

rheumatoid arthritis, a comparable immune-mediated inflammatory disease with regard to pathogenesis, stressors and treatment. Besides, IBD studies that used a generic, though validated coping questionnaire failed to identify relevant coping strategies. Fourth, although we adjusted for the most important confounders, such as gender and clinical disease activity, residual confounding cannot be completely excluded.

If these limitations are taken into consideration, we feel that this prospective study provides valuable data for clinical practice. Arthropathies are the most common extra-intestinal manifestation in IBD, leading to significant morbidity, disability, and societal costs. Recently, it has been reported that self-reported joint pain is a major predictor of work disability in patients with IBD.[50] Work disability is major cost driver, accounting for 18–69% of overall costs in IBD.[51-52] Thus, adequate treatment of back/joint pain may lead to reduced work disability and associated costs. Nevertheless, many patients with IBD-associated arthropathy remain undiagnosed.[53] Apart from providing these patients with the appropriate medical treatment, their QoL and work productivity can be further improved by behavioral interventions. These interventions should be aimed at eliciting and addressing patients' illness perceptions and stimulating adaptive coping strategies. Previous studies have already shown that behavioral interventions based on the Common Sense Model can change illness perceptions and coping strategies of patients after myocardial infarction and patients with end-stage renal disease, and thereby improve major components of QoL (e.g. return to work).[54-57]

In conclusion, back/joint pain persistently and negatively impacted the QoL and work productivity of patients with IBD-associated arthropathy. Illness perceptions and coping also had a significant impact on QoL and work productivity. As potentially modifiable factors, illness perceptions and coping may provide additional targets for behavioral interventions, aimed at improving QoL and increasing work productivity. Multidisciplinary teams, incorporating such interventions, are warranted.

REFERENCES

1. 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.
2. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss Inflammatory Bowel Disease Cohort. Am J Gastroenterol 2011;106:110–19.
3. Palm O, Bernklev T, Moum B, et al. 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. D'Incà R, Podswiadek M, Ferronato A, et al. Articular manifestations in inflammatory bowel disease patients: a prospective study. Dig Liver Dis 2009;41:565–69.
6. Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001;96:1116–22.
7. Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World J Gastroenterol 2003;9:2300–7.
8. Lanna CC, Ferrari ML, Rocha SL, et al. A cross-sectional study of 130 Brazilian patients with Crohn's disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations. Clin Rheumatol 2008;27:503–9.
9. Turkcapar N, Toruner M, Soykan I, et al. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatol Int 2006;26:663–68.
10. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860–65.
11. Siebert U, Wurm J, Gothe RM, et al. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the Swiss inflammatory bowel disease cohort study. Inflamm Bowel Dis 2013;19:847–55.
12. Picavet HSJ, Schouten JSAG. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC3-study. Pain 2003;102:167–78.
13. Hagger MS, Orbell S. A meta-analytic review of the Common Sense Model of illness representations. Psychol Health 2003;18:141–84.
14. Leventhal H, Brissette I, Leventhal EA. The Common-Sense Model of self-regulation of health and illness. Cameron LD Leventhal H. The Self-Regulation of Health and Illness Behaviour. London: Routledge; 2003:42–65.
15. Vaughan R, Morrison L, Miller E. The illness representations of multiple sclerosis and their relations to outcome. Br J Health Psychol 2003;8:287–301.
16. Scharloo M, Kaptein AA, Weinman J, et al. Illness perceptions, coping and functioning in patients with rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis. J Psychosom Res 1998;44:573–85.
17. Dorrian A, Dempster M, Adair P. Adjustment to inflammatory bowel disease: the relative influence of illness perceptions and coping. Inflamm Bowel Dis 2009;15:47–55.

18. Han SW, McColl E, Barton JR, et al. Predictors of quality of life in ulcerative colitis. The importance of symptoms and illness representations. Inflamm Bowel Dis 2005;11:24–34.
19. Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to inflammatory bowel disease. Inflamm Bowel Dis 2010;16:1685–95.
20. Knowles SR, Wilson JL, Connell WR, et al. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the common sense model of illness. Inflamm Bowel Dis 2011;17:2551–57.
21. Taft TH, Keefer L, Artz C, et al. Perceptions of illness stigma in patients with inflammatory bowel disease and irritable bowel syndrome. Qual Life Res 2011;20:1391–99.
22. Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. J Health Psychol 2013;18:972–83.
23. Van der Have M, Minderhoud IM, Kaptein AA, et al. Substantial impact of illness perceptions on quality of life in patients with Crohn's disease. J Crohns Colitis 2013;7(8):292-301.
24. Knowles SR, Gass C, Macrae F. Illness perceptions in IBD influence psychological status, sexual health and satisfaction, body image and relational functioning: a preliminary exploration using Structural Equation Modeling. J Crohns Colitis 2013;7:344–50.
25. Knowles SR, Cook SI, Tribbick D. Relationship between health status, illness perceptions, coping strategies and psychological morbidity: a preliminary study with IBD stoma patients. J Crohns Colitis 2013;7:471–78.
26. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127–32.
27. 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;27:361–68.
28. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1:876.
29. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29–32.
30. Moss-Morris R, Weinman J, Petrie K. The revised Illness Perception Questionnaire (IPQ-R). Psychol Health 2002;17:1–16.
31. Van Lankveld W, Näring G, van der Staak C, et al. De ontwikkeling van de CORS. Coping met Reuma Stressoren. Gedrag en Gezond 1993;21:40–48.
32. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol 1996;91:1571–78.
33. Han SW, Gregory W, Nylander D, et al The SIBDQ: further validation in ulcerative colitis patients. Am J Gastroenterol 2000;92:145–51.
34. Ware JE, Sherbourne CA. The MOS 36-item Short-Form health survey (SF 36). Conceptual framework and item selection. Med Care 1992;30:473–83.
35. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–65.
36. Reilly MC, Gerlier L, Brabant Y, et al. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. Clin Ther 2008;30:393–404.
37. Van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta-analysis. J Crohns Colitis 2014;8:93–106.
38. Lazarus RS. Psychological stress and coping in adaptation and illness. Int J Psychiatry Med 1974;5:321–33.

39. Lazarus RS. Coping theory and research: past, present, and future. Psychosom Med 1993;55:234–47.
40. McCombie AM, Mulder RT, Gearry RB, et al. How IBD patients cope with IBD: a systematic review. J Crohns Colitis 2013;7:89–106.
41. Jones MP, Wessinger S, Crowell MD. Coping strategies and interpersonal support in patients with irritable bowel syndrome and inflammatory bowel disease. Clin Gastroenterol Hepatol 2006;4:474–81.
42. Graff LA, Walker JR, Clara I, et al Stress coping, distress, and health perceptions in inflammatory bowel disease and community controls. Am J Gastroenterol 2009;104:2959–69.
43. Van Lankveld W, Näring G, van 't Pad Bosch P, et al. Behavioral coping and physical functioning: the effect of adjusting the level of activity on observed dexterity. J Rheumatol 1999;26:1058–64.
44. Evers AW, Kraaimaat FW, Geenen R, et al. Pain coping and social support as predictors of long-term functional disability and pain in early rheumatoid arthritis. Behav Res Ther 2003;41:1295–310.
45. Scharloo M, Kaptein AA, Weinman JA, et al. Predicting functional status in patients with rheumatoid arthritis. J Rheumatol 1999;26:1686–93.
46. Chorus AM, Miedema HS, Boonen A, et al. Quality of life and work in patients with rheumatoid arthritis and ankylosing spondylitis of working age. Ann Rheum Dis 2003;62:1178–84.
47. Vlaeyen JW, Kole-Snijders AM, Boeren RG, et al. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain 1995;62:363–72.
48. Dekker J, Boot B, van der Woude LH, et al. Pain and disability in osteoarthritis: a review of biobehavioral mechanisms. J Behav Med 1992;15:189–214.
49. Kottke FJ. The effects of limitation of activity upon the human body. JAMA 1966;196:825–30.
50. Van der Valk ME, Mangen MJ, Leenders M, et al. Risk factors of work disability in patients with inflammatory bowel disease – a Dutch nationwide web-based survey. J Crohns Colitis 2013;8:590–97.
51. Van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. Gut 2014;63:72–79.
52. Yu AP, Cabanilla LA, Wu EQ, et al. The costs of Crohn's disease in the United States and other Western countries: a systematic review. Curr Med Res Opin 2008;24:319–28.
53. Stolwijk C, Pierik M, Landewé R, et al. Prevalence of self-reported spondyloarthritis features in a cohort of patients with inflammatory bowel disease. Can J Gastroenterol 2013;27:199–205.
54. Petrie KJ, Cameron LD, Ellis CJ, et al. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. Psychosom Med 2002;64:580–86.
55. Broadbent E, Ellis CJ, Thomas J, et al. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. J Psychosom Res 2009;67:17–23.
56. Karamanidou C, Weinman J, Horne R. Improving haemodialysis patients' understanding of phosphate-binding medication: a pilot study of a psycho-educational intervention designed to change patients' perceptions of the problem and treatment. Br J Health Psychol 2008;13:205–14.
57. Jansen DL, Heijmans M, Rijken M, et al. The development of and first experiences with a behavioural self-regulation intervention for end stage renal disease patients and their partners. J Health Psychol 2011;16:274–83.

TABLES AND FIGURES

Table 1. Demographic and clinical variables of the study population.

Variable	IBD patients (n=204)
Type of IBD, n (%)	
Crohn's disease	146 (71.6)
Ulcerative colitis	58 (28.4)
Age (years), mean (SD)	44.3 (13.7)
Male gender, n (%)	82 (40.2)
Current smoker, n (%)	47 (23.0)
Disease duration (years), median (IQR)	15.0 (7.0-24.0)
Employed, n (%)	128 (62.6)
Montreal classification	
Location CD, n (%)	
L1 ileal	36 (24.7)
L2 colonic	33 (22.6)
L3 ileocolonic	65 (44.5)
L1-3 + L4 upper	12 (9.5)
Behaviour CD, n (%)	
B1 non-stricturing/penetrating	62 (42.5)
B2 stricturing	22 (15.1)
B3 penetrating	21 (14.4)
+ perianal disease	41 (28.1)
Extension UC, n (%)	
E1 ulcerative proctitis	4 (6.9)
E2 left sided UC	20 (34.5)
E3 extensive UC (pancolitis)	34 (58.6)
Current medication use, n (%)	
5-ASA	44 (21.6)
Steroids	10 (4.9)
Immunomodulators	45 (22.1)
Anti-TNF agents	56 (27.5)
Axial and/or peripheral joint complaints, n (%)	113 (55.5)
Peripheral joint complaints only	41 (36.3)
Back pain only	8 (7.1)
Mixed complaints	64 (56.6)
Distribution (painful) peripheral joints, n (%)	
Monoarticular	15 (14.3)
Oligoarticular	45 (42.9)
Polyarticular	45 42.9)
Enthesitis[a], n (%)	2 (1.0)
Dactylitis[a], n (%)	2 (1.0)
Extra-intestinal manifestation[b], n (%)	49 (24.0)
Elevated C-reactive protein, n (%)	30 (14.7)
Elevated erythrocyte sedimentation rate, n (%)	42 (20.9)
HLA-B27[c], n (%)	7 (5.9)
Sacroilitis on X-ray[d], n (%)	5/123 (4.1)

[a] reference 26; [b] skin: psoriasis, erythema nodosum, pyoderma gangrenosum. joint: arthritis, dactylitis, heel enthesitis, ankylosing spondylitis, eye: acute anterior uveitis (current or past); [c] HLA-B27 status was available in 118 patients; [d] results of X-ray were available in 123 patients. IQR: Inter Quartile Range.

Table 2. Linear mixel model with SIBDQ as outcome variable and demographic/clinical variables (step 1), illness perceptions (step 2), and coping (step 3) as independent variables.

	Quality of life	
Predicting variables	**Beta**	**95% CI**
Step 1: Demographic & clinical variables		
Disease activity	-1.17***	-1.41 to -0.93
Joint pain	-1.04***	-1.40 to -0.68
Step 2: Illness perceptions		
Identity	-0.17	-0.48 to 0.14
Consequences	-0.39***	-0.59 to -0.18
Personal control	-0.08	-0.27 to 0.10
Illness coherence	0.14	-0.08 to 0.35
Timeline cyclical	-0.36**	-0.63 to -0.10
Emotional representations	-0.47***	-0.66 to -0.28
Step 3: Coping		
Decreasing activity	-0.26	-0.48 to -0.03
Pacing	0.11	-0.06 to 0.28

* = p value <0.05, ** = p value <0.01, *** p value <0.001. SIBDQ = Short Inflammatory Bowel Disease Questionnaire.

Table 3. Linear mixed models with SF-PCS and SF-MCS as outcome variables and demographic/clinical variables (step 1), illness perceptions (step 2), and coping (step 3) as independent variables.

	PCS		MCS	
Predicting variables	**Beta**	**95% CI**	**Beta**	**95% CI**
Step 1: Demographic & clinical characteristics				
Gender	-	-	-0.90	-2.84 to 1.03
Disease activity	-0.63***	-0.84 to -0.42	-0.58***	-0.84 to -0.31
Joint pain	-1.69***	-2.00 to -1.38	-0.48*	-0.87 to -0.10
Step 2: Illness perceptions				
Identity	-0.34*	-0.62 to -0.06	-0.01	-0.34 to 0.31
Consequences	-0.59***	-0.77 to -0.40	-0.21	0.42 to 0.00
Personal control	0.20*	0.03 to 0.37	0.09	-0.11 to 0.29
Illness coherence	-	-	0.30**	0.08 to 0.52
Timeline cyclical	-	-	-0.04	-0.32 to 0.23
Emotional representations	0.08	-0.07 to 0.24	-0.72***	-0.93 to -0.52
Step 3: Coping				
Decreasing activity	-0.21*	-0.41 to -0.01	-0.42**	-0.66 to -0.18
Pacing	-0.17	-0.35 to 0.00	0.23	-0.05 to 0.51
Creative solutions	-	-	0.03	-0.16 to 0.22

* = p value <0.05, ** = p value <0.01, *** p value <0.001. SF-36-PCS = Short Form-36 Physical Component Score, SF-36-MCS = Short Form-36 Mental Component Score.

Table 4. Linear mixed model with work productivity and activity impairment (WPAI) as outcome variables and demographic/clinical variables (step 1), illness perceptions (step 2), and coping (step 3) as independent variables.

	Work productivity		Activity impairment	
Predicting variables	**Beta**	**95% CI**	**Beta**	**95% CI**
Step 1: Demographic & clinical characteristics				
Gender	-	-	0.26	-0.22 to 0.75
Disease activity	0.41***	0.29 to 0.53	0.19***	0.12 to 0.25
Joint pain	0.22**	0.07 to 0.37	0.48***	0.39 to 0.58
Step 2: Illness perceptions				
Identity	0.05	-0.08 to 0.19	0.10*	1.01 to 0.19
Consequences	0.14*	0.06 to 0.22	0.13***	0.07 to 0.18
Personal control	-	-	-0.03	-0.08 to 0.02
Illness coherence	-0.08	-0.17 to 0.01	0.01	-0.05 to 0.07
Timeline cyclical	-0.00	-0.11 to 0.10	0.02	-0.06 to 0.09
Emotional representations	0.04	-0.04 to 0.12	0.06*	0.01 to 0.12
Step 3: Coping				
Decreasing activity	0.07	-0.02 to 0.16	0.10**	0.04 to 0.17
Pacing	0.04	-0.04 to 0.11	0.02	-0.03 to 0.07

* = p value <0.05, ** = p value <0.01, *** p value <0.001. WPAI = Work Productivity Activity Impairment.

Figure 1. Study flow-chart.

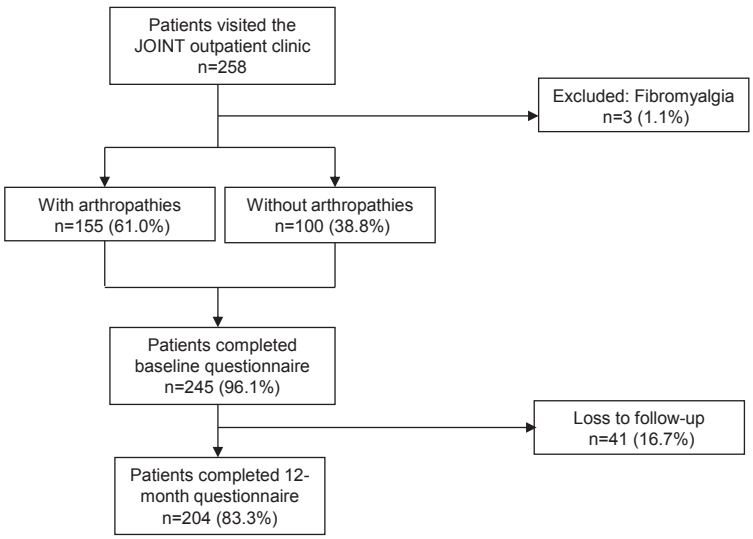
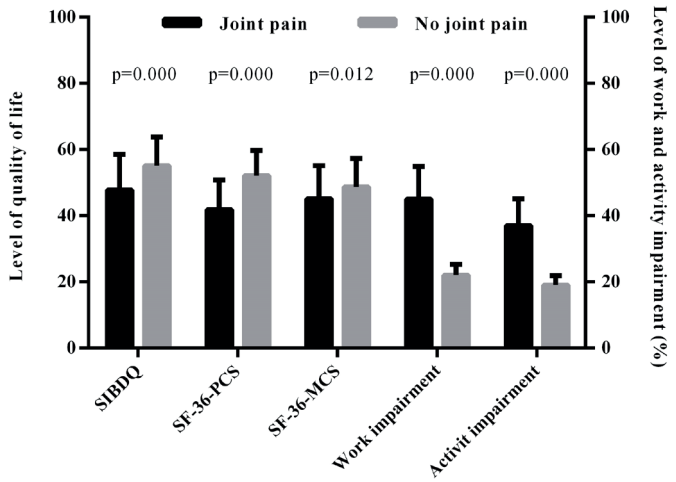


Figure 2. Mean baseline levels of generic quality of life (SF-36–PCS, SF-36–MCS), disease-specific quality of life (SIBDQ), Work and Activity Impairment (WPAI) in IBD patients with (n=113) and without (n=91) joint pain.



CHAPTER 8

Cerebral magnetic resonance imaging in quiescent Crohn's Disease patients with fatigue

S.J.H. van Erp, E.A. Ercan, P. Breedveld, L.K.P.M. Brakenhoff, E. Ghariq, S. Schmid, M.J.P van Osch, M.A. van Buchem, B.J. Emmer, J. van der Grond, R. Wolterbeek, D.W. Hommes, H.H. Fidder, N.J.A van der Wee, T.W.J. Huizinga, D. van der Heijde, H.A.M Middelkoop, I. Ronen, A.E. van der Meulen-de Jong

World Journal of Gastroenterology, 2017

ABSTRACT

Background: This pilot study evaluates brain involvement in quiescent Crohn's Disease (CD) patients with fatigue using quantitative Magnetic Resonance Imaging (MRI).

Methods: Multiple MRI techniques were used to assess cerebral changes in 20 quiescent CD patients with fatigue (defined with at least 6 points out of an 11-point numeric rating scale (NRS)) compared with 17 healthy age and gender matched controls without fatigue. Furthermore, mental status was assessed by cognitive functioning, based on the neuropsychological inventory (NPI) including the different domains global cognitive functioning, memory and executive functioning and in addition mood and quality of life scores. Cognitive functioning and mood status were correlated with MRI findings in the both study groups.

Results: Reduced glutamate + glutamine (Glx = Glu + Gln) concentrations ($p=0.02$) and ratios to total creatine ($p=0.02$) were found in CD patients compared with controls. Significant increased Cerebral Blood Flow (CBF) ($p=0.05$) was found in CD patients (53.08±6.14 ml/100g/min) compared with controls (47.60±8.62 ml/100g/min). CD patients encountered significantly more depressive symptoms ($p<0.001$). Cognitive functioning scores related to memory ($p = 0.007$) and executive functioning ($p=0.02$) were lower in CD patients and both scores showed correlation with depression and anxiety. No correlation was found subcortical volumes between CD patients and controls in the T_1-weighted analysis. In addition, no correlation was found between mental status and MRI findings.

Conclusion: This work shows evidence for perfusion, neurochemical and mental differences in the brain of CD patients with fatigue compared with healthy controls.

INTRODUCTION

Crohn's disease (CD) is a relapsing inflammatory bowel disease (IBD)[1], characterized by segmental transmural lesions that can affect any part of the gastrointestinal tract.[2] Besides gastrointestinal symptoms, fatigue is common in CD patients. In contrast to regular fatigue which affects nearly everyone, disease-related fatigue is more long lasting and may occur despite sufficient sleep and rest. Generally, fatigue lasting for more than 6 months is considered chronic and is significantly more prevalent in IBD patients than in healthy controls.[3] Although fatigue is influenced by IBD disease activity, 40% of the patients with quiescent disease report fatigue as well and contributes negatively to the patients' health-related quality of life (QoL).[4-5]

The pathogenesis of CD is multifactorial and results from an impaired interaction between environment, commensal microbiota and the human immune system, leading to a chronic inflammatory status and eventually CD.[6-7] Furthermore, in both quiescent and active CD patients increased levels of circulating inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) are reported.[8-10] Although quiescent CD patients report fewer clinical symptoms and score less on the clinical activity score compared with active CD patients, inflammatory cytokines are present.[9-10] TNF-α can be secreted by a large variety of cells[8] and can initiate a signalling stimulus to the brain parenchyma that will subsequently activate microglia. Activated microglia stimulates the production of monocyte chemo-attractant protein (MCP)-/CCP2, which recruits monocytes into the brain.[9-11] Moreover, this cerebral infiltration of monocytes plays an important role in driving inflammation in the brain.[11-13]

Magnetic Resonance Imaging (MRI) is an imaging technique widely used to visualize the effect of several neurological diseases, such as Multiple Sclerosis (MS), Parkinson's Disease and Alzheimer disease, in the brain.[14] A variety of MRI methods can be employed to identify cerebral changes due to a specific disease. These methods include T_1-weighted imaging, magnetization transfer imaging (MTI), magnetic resonance spectroscopy (MRS), arterial spin labeling (ASL) and diffusion tensor imaging (DTI). T_1-weighted imaging provides high-resolution, high-contrast anatomical images of the brain and can be used to determine the volumes of the grey matter (GM), white matter (WM), cerebral spinal fluid (CSF) and subcortical structures.[15] Through voxel based morphometry (VBM), it is possible to visualize local changes in GM volumes.[16] MTI is a technique sensitive

to brain tissue microstructural changes, stemming from changes in macromolecules such as myelin or cell membranes.[17] MRS measures the concentration of certain metabolites in living tissues and gives evidence for neurochemical changes.[18] ASL is a non-invasive tool for the quantification of regional cerebral blood flow (CBF)[19] and can reveal changes in tissue perfusion. DTI is sensitive to minute changes in tissue microstructure, such as changes in myelin integrity and axonal density in white matter fiber tracts, based on the random motion or diffusion of water molecules.[20]

Previous MRI studies have shown that systemic inflammation contributes to cognitive decline, for example in relation to aging,[21] but also to brain diseases including Alzheimer disease, MS and Parkinson's disease by promoting activation of the immune system.[22-24] Metabolic and cerebral perfusion changes have been found in the brain of patients with Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc) and Systemic Lupus Erythematosus (SLE).[11,12,25-32] In addition, previous studies performed in patients with Chronic Fatigue Syndrome (CFS) found an association between fatigue complaints and metabolic changes in the brain as well.[33-35] In CFS patients, the mean ratio of choline (Cho) to creatine (Cr) in the occipital cortex was significantly higher than in controls, indicating an abnormality of phospholipid metabolism in the brain in CFS.[33-34] These findings suggest that systemic inflammation and fatigue complaints could have structural, neurochemical and functional correlates in the brain. So far, the link between systemic inflammation, disease-induced fatigue and changes in the brain have not been explored in CD patients. The aim of this exploratory study was to investigate to what extent systemic inflammation affects the brain of quiescent CD patients, by using a variety of MRI acquisition methods and neuropsychological examinations that assess cognition, mood and QoL. Furthermore, the correlation between MRI changes, clinical characteristics, including fatigue scores, and mental status was investigated.

MATERIALS AND METHODS

Study population and study design

In this case-control study 20 CD patients and 17 age and gender matched healthy controls were included. Since it is known from literature that there is an age associated decrease in brain volume, primarily caused by a decrease in neuronal size and partly due to a reduction in numbers of neurons caused

by apoptosis[36], a correction was made for this confounder by matching the subjects.

Consecutive CD patients, fulfilling the inclusion criteria, were recruited through the IBD outpatient clinic of the department of Gastroenterology and Hepatology of the Leiden University Medical Center (LUMC), the Netherlands. The patients had endoscopic proven CD for at least 3 months before inclusion, were in clinical remission and experienced fatigue. CD patients with anemia (Hb<7.0 mmol/L), primary sclerosing cholangitis (PSC) and routine MRI-contraindications (e.g. instable metal implants or a pacemaker) were excluded. All medication deemed necessary by the gastroenterologist was allowed at study inclusion, except for anti-TNFα or corticosteroid use, since this medication could reduce systemic inflammation the most and thus influence clinical disease activity. Healthy controls were recruited via an advertisement in het LUMC and included in the study if they had no anamnestic brain abnormalities, nervous system disease or chronic inflammation in the body. A 1-day program was set up for all participants by the relevant medical specialists, including a gastroenterologist, radiologist, psychiatrist and neuropsychologist and all individuals were asked to complete several questionnaires at study inclusion about demographics, mental status and QoL. This study was approved by the institutional medical ethical committee of the LUMC and all patients signed a written informed consent prior to study enrolment.

Clinical characteristics

Disease activity

The clinical disease activity of the CD patients was measured with the Harvey-Bradshaw Index (HBI). The HBI consists of 12 criteria, which include general well-being, abdominal pain, daily number of liquid stools, abdominal mass and extra-intestinal manifestations (arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula and abscess). Patients with an HBI score of 4 or less were classified as having quiescent CD disease.[37]

Fatigue

Fatigue was assessed with the Multidimensional Fatigue Index (MFI) and the Visual Analogue Scale (VAS). The MFI is a self-report measurement containing 20 questions consisting of 5 subscales covering different dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. The questions are about the fatigue experienced by the subject in the

7 days prior to examination. Scores range from 4 to 20, with higher scores indicating higher levels of fatigue.[38] The VAS consists of a 10 point self-rating scale that measures subjective experiences of fatigue. The participants had to indicate on a visual line how they were currently feeling. Six points or more indicated the presence and experience of fatigue in individuals.[39]

MRI Data Acquisition

All study subjects underwent MRI of the brain, using a Philips Ingenia 3.0 Tesla MRI Scanner (Philips Medical Systems, Best, the Netherlands) equipped with a 12 channel head coil, and images were evaluated by an experienced neuroradiologist (MvB). The MRI protocol consisted of T_1-weighted imaging, MTI, MRS, ASL and DTI, and lasted for about 60 minutes. Since more CD patients were included and all patients and healthy controls were age-gender matched, in total 3 CD patients, who matched the least with the controls, got excluded from the voxel-based analysis of the T_1-weighted and DTI data. For the MRS and ASL analyses data of some CD subjects were either missing because of time limitations or excluded due to low quality, caused by subject motion. For the MRS analysis only 9 CD patients and 9 age and gender matched controls were included, and for the ASL analysis 16 CD patients and 16 age and gender matched controls were included (Figure 1). The MRI scan protocol consisted of (a) Axial 3D T1-weighted images (FOV: 224x144x182, resolution: 0.88x0.88x1.20 mm^3, TR/TE=9.75/4.59 ms); (b) Sagittal FLAIR images (FOV: 224x144x180, resolution: 0.5x0.5x3.6 mm^3, TR/TE/TI = 10000/120/1650 ms); (c) Axial Diffusion Tensor Images (DTI) (FOV: 176x144x224, resolution: 1.75x1.75x3.6 mm^3, TR/TE = 4317/55.33 ms, one volume with b = 0 s/mm^2 and 32 diffusion-weighted volumes with b = 800 s/mm^2); (d) Axial MTI (FOV: 224x144x180, resolution: 0.88x0.88x7.2 mm^3, TR/TE = 100/10.95 ms, two volumes acquired one with and one without a radiofrequency saturation pulse) (e) Arterial Spin Labeling (ASL) (FOV: 240x240x133, resolution: 3.0x3.0x7.0 mm^3, TR/TE = 4000/15.19 ms, labeling duration = 1650 ms, post-labeling delay = 1525 ms, 35 label and control pairs and background suppression inversion pulses at 50 and 1150 ms); (f) A single volume, stimulated echo acquisition mode (STEAM) ^{1}H MRS scan with a volume of interest (VOI) located in the left centrum semi ovale, containing mostly white matter as shown in Figure 2, (voxel size = 30x15x15mm^3, TR/TE = 2000/14 ms, mixing time = 19 ms, sample size = 2048, number of averages = 96).

Post-processing and data analysis

T_1-weighted image analysis

Brain extraction tool (BET) of FMRIB Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) was used to extract the brain tissue from T_1-weighted images.[15] FSL FMRIB's Automated Segmentation Tool (FAST)[40] was used to segment GM, WM and CSF tissues from the brain extracted T_1-weighted images. FSL FMRIB's Integrated Registration and Segmentation Tool (FIRST) was used to segment subcortical structures: nucleus accumbens, amygdala, caudate, hippocampus, globus pallidus, putamen and thalamus.[41] Following segmentation, the volumes of GM, WM and subcortical structures were calculated using FSL Maths. The volumes were normalized to subject intracranial volume by dividing the volumes with the total brain volume of the same subject. VBM in FSL was used to assess local GM differences between CD patients and controls.[16,42]

Magnetization Transfer Images analysis

MTI were split into images with and without saturation. Both images, with and without saturation, were brain extracted with BET and the image without saturation was aligned to the image with saturation. After alignment, the magnetization transfer ratio (MTR) of the whole brain was calculated using FSL Maths. The MTR images were then registered to the T_1-weighted images from the same subject with FLIRT.[43] Subsequently, MTR images were multiplied with the binary GM and WM masks from the same subject, to create GM and WM MTR images. Tissue-specific histograms of MTR values from the GM and WM of patients and controls were created using an in house-developed MATLAB® program (Mathworks, Natick, MA, USA).

MR Spectroscopy analysis

The MRS analysis was performed in MATLAB and LCmodel.[44] An in-house developed MATLAB code was used to calculate and correct for GM, WM and CSF tissue fraction (%) within the VOI for each subject separately. LCmodel was used for the calculation of the concentration and ratio to total creatine (tCr) of the metabolites N-acetyl-aspartate (NAA), creatine (Cr), glutamate (Glu), myo-inositol (Ins), glutamine (Gln), N-acetyl-aspartyl-glutamate (NAAG) and choline (Cho). Institutional units (IU) of concentration were expressed in mmol. Among these metabolites, NAA is a neuronal marker, NAAG is suggested to be related to excitatory neurotransmission, total Creatine (tCr), the sum of phosphocreatine and creatine, is a marker of energy metabolism. Cho is related to cell membrane turnover, Glu is an excitatory neurotransmitter predominantly found in

neurons, Gln is a precursor for Glu and found mostly in astrocytes, and Ins is a possible astrocytic marker.[45] The mean ratios of NAA, Glu, Ins, Gln, NAAG and Cho to tCr were compared between the two study groups.

Arterial Spin Labeling analysis

The average GM Cerebral Blood Flow (CBF) value was calculated in FSL.[46] The ASL label and control images were motion corrected by FSL MCFLIRT.[47] The perfusion maps were calculated for each subject by subtracting the label from the control images and averaging those images. Following that, perfusion maps from each subject were registered first linearly and then nonlinearly to GM volume segmented from the T_1-weighted image of the subject and subsequently they were first linearly and then nonlinearly registered to average brain template from the Montreal Neurological Institute (MNI). CBF of the GM is calculated by using a binary GM mask of the subject with a threshold of 60% GM probability and using the following equation:

$$CBF_{pCASL} = \frac{6000 \cdot \lambda \cdot \Delta M \cdot e^{(PLD/T_{1a})}}{SI_{PD} \cdot 2 \cdot \alpha_{pCASL} \cdot T_{1a} \cdot \alpha_{BSup} \cdot (1 - e^{-(\tau/T_{1a})})}$$

where λ is the blood/brain partition coefficient in mL/g which was 0.9, ΔM is the signal intensity of the control image subtracted with the signal intensity of the label image, the post labelling delay (PLD) was 1525 ms. T_1a is the longitudinal relaxation time of the blood was 1664 ms, SI_{PD} is the signal intensity of a proton density-weighted image and τ is the label duration which was 1650 ms. A_{pCASL} is the labelling efficiency, which was 0.85 and α_{BSup} was 0.83. A comparison of GM CBF was made between the patients and controls.

Diffusion Tension Images analysis

ExploreDTI software[48] was used for motion and distortion correction of the DTI images and for calculating the Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps. FA and MD maps were used as an input to tract-based spatial statistics (TBSS) processing[49], which was carried out in FSL. The FA maps were first linearly registered with an affine transformation, subsequently non-linearly registered to the MNI space, and a mean FA skeleton was created. For each subject, the FA map was projected on the skeleton. Following that, randomisation was used to perform t-test based voxel-wise comparison of the FA skeletons between patients and controls. The same procedure was repeated for MD maps.

Assessment of cognitive performance

Cognition

Several neuropsychological assessments were conducted in both healthy controls and CD patients and evaluated by an experienced clinical neuropsychologist (HM). The examination took approximately one hour and included validated test methods in a fixed order. Since the cognitive functioning of patients with IBD has not been fully previously investigated, the focus was on a wide range of neuropsychological functions. Global cognitive functioning was assessed by the Minimal Mental State Examination (MMSE). The MMSE contained 11 questions, subdivided into 5 subdomains. All questions were scored individually and added to produce a total score ranging from 0 to 30, with higher scores indicating better cognitive functioning.[50] The memory domain was evaluated with the Digit Span Forward and Backward subtests of, respectively the revised Wechsler Adult Intelligence Scale (WAIS-R)[51] and the revised Wechsler Memory Scale (WMS-R). Higher scores reflected better memory performance.[52] Executive functioning was assessed by the Word Fluency Test (WFT)[53], Stroop-Color-Word test (SCWT)[54] given in three parts, and the Trail Making Test (TMT)[55] subdivided into two parts, whereby part A measured attention and performance speed, and part B measured mental flexibility and ability to shift attention. The TMT involved scanning, visuomotor tracking, divided attention and cognitive flexibility. The time used for each trial was noted, with more time used indicating lower performance. The SCWT was used to measure interference sensibility. One response (reading the word) should be inhibited in order to name the colour of the ink, which leads to a delay in reaction time. The number of correct responses within 45 seconds was counted.[54] Furthermore, the WAIS-R Digit symbol and Digit cancellation test was measured.[51]

Mental status

Cognitive performance depends on the psychiatric status of the patient[56], and therefore the HADS (Hospital Anxiety Depression Scale) was included in the neuropsychological examination. The HADS was used to determine depressive symptoms and anxiety. HADS is a widely used measurement to identify emotional disorders in non-psychiatric patients. The scale includes 14 items, 7 items concerning anxiety and 7 concerning depression, each scored between 0 and 3. A score above 8 on each individual scale were considered as a possible case and a score above 10 as a probable case.[57]

Quality of life

To determine the quality of life, the Short Form-36 (SF-36) was used. The SF-36 is a generic questionnaire to assess self-reported quality of life. This measurement includes in total 8 subscales covering physical and mental aspects of QoL. The score ranges from 0 to 100, with higher score indicating better QoL. The Dutch translation of the SF-36 was validated in both the general population and in CD patients.[58]

Statistics

Data analyses were performed using SPSS 20.0, IBM Corp, 2011, Armonk, NY, US. Descriptive statistics were used for the patients' characteristics. All comparisons between the patient and control groups were performed with an independent T-test. A p-value ≤0.05 was considered statistically significant. To correct for multiple testing, the level of significance was set at $p<0.01$ (0.05/5) and $p<0.006$ (0.05/8) for the fatigue (five MFI subscores) and QoL (eight SF-38 subscales) scores, respectively. Based on the individual cognitive tests corrected for education, Z-scores of the different cognitive domains were created by using the Unianova test with an average mean and standard deviation (SD). Correlations between the MRI outcomes, cognition and mood status were performed with the Pearson Correlation test.

RESULTS

Demographic characteristics

In this study, 20 CD patients and 17 healthy controls were age ($p=0.46$) and gender matched ($p=0.68$). All patients were in clinical remission at study inclusion (mean HBI=2.16, SD=1.12), with an average age of onset at 21.4 years and an IBD disease duration of 8.8 years. Based on the inclusion criteria, patients reported more fatigue complaints according to the MFI-20 ($p<0.001$) and VAS fatigue score ($p<0.001$) compared with the control subjects. Furthermore, the education level of the healthy controls was significantly higher than that of the CD patients. Since this variable might influence mental status scores, a correction was made. An overview of the clinical characteristics of the individuals is presented in Table 1.

MRI analysis

Volumetric data: The comparison of the subcortical volumes between the CD patients and controls in the analysis of the T_1weighted images did not show significant differences between the two subject groups. The volume differences in the right amygdala (p=0.08) and nucleus accumbens (p=0.08) just missed significance (Table 2). VBM analysis showed a lower GM content in the superior frontal gyrus in CD patients compared with healthy controls (p<0.05) (Figure 3).

MTI data: No significant differences were observed in the mean MTR values or in the MTR histogram peak heights of the CD patients compared with healthy controls.

MRS data: Lower glutamate + glutamine (Glx = Glu + Gln) concentrations (4.85±0.78 mmol vs 5.96±0.98 mmol, p=0.02) and ratios to tCr (0.92±0.13 vs 1.10±0.14, p=0.02) were found in the patient population compared with control subjects (Table 3).

ASL data: Average GM CBF of the CD patients (53.1±6.1 ml/100g/min) was significantly higher than the GM CBF of the control group (47.6±8.6 ml/100g/min) (p=0.05).

DTI data: No differences were observed across white matter in the FA and MD values between CD patients and controls.

Mental status

Neuropsychological examination and cognitive scores were corrected for educational level (Table 4). Generally, a difference close to significance between patients and controls was found in several individual cognitive test scores. Compared with controls, CD patients had a lower Stroop interference index (p=0.06), a reduced total score of the WAIS-R Digit Symbol test (p=0.06) and were slower in completing trial A of the TMT test (p=0.08). When the individual tests were transformed into a Z-score based on the different cognitive domains, significant reduced Z-scores of the memory domain (p=0.007) and executive functioning domain (p=0.02) were found in the patient population compared with the healthy controls (Table 5). CD patients experienced more depressive symptoms (p<0.001), were more anxious (p=0.002) and reported a significantly lower QoL.

Correlation of MRI findings with clinical characteristics and mental status
No correlations were found between mental status, including depression and anxiety, and MRI findings. Depressive symptoms were correlated with reduced scores of global cognitive functioning (p=0.003), memory (p=0.04) and executive functioning (p=0.04). Additionally, CD patients reported in the present study increased symptoms of anxiety and this was significantly correlated with reduced global cognitive functioning (r = -0.36, p=0.03) and memory scores (p=0.05). No further correlations between cognitive scores, disease activity, disease duration and MRI findings were found in this study.

DISCUSSION

Several MRI techniques were used in this study in a cross-sectional manner to examine the differences in brain morphology, neurochemistry and perfusion between CD patients with fatigue and healthy controls without fatigue. The most important findings reported in this study are the significant differences in perfusion, neurochemistry and mental status (e.g. cognition, mood and QoL) between patients and controls. Lower levels of Glx concentration and their ratio to tCr were observed and an increased CBF was found in the patient population compared with control subjects. CD patients scored lower on several individual cognitive test scores, with a trend towards significance, and scored significantly lower on the memory and the executive functioning domain compared with the healthy controls. Also, the patient population had a significantly lower QoL and mood status.

The present study observed with MRS a significantly reduced Glx concentration as well as a lower ratio of Glx to tCr in the CD group. Glutamate is the predominant excitatory neurotransmitter in the brain and is involved in different brain functions including memory and mood status. Receptors are mainly present in the hippocampus.[59-60] Glutamine is important in energy metabolism of the brain and previous studies reported that a reduced level of glutamine is associated with brain diseases such as Alzheimer.[61-21] Increasing evidence shows that major depression disorder (MDD) is associated with altered function of the major excitatory and inhibitory neurotransmitters such as glutamate and GABA.[63-64] The present study did not find correlations between depressive symptoms and the reduced Glx concentration and ratio to tCr.

These reduced MRS results found in the present pilot study in CD patients are not in accordance with the findings of previous research performed in other inflammatory diseases such as RA and SLE.[11,65] RA and SLE patients were shown to have increased choline and myo-inisotol levels, indicating inflammation in the form of monocyte infiltration since this is a marker of cell membrane turnover.[66-67] In addition, in SLE patients only decreased NAA signals were reported, indicating neuronal loss[68-70], while an increased NAA ratio was found in our CD patient population. This contradiction may be due to the fact that RA and SLE are systemic inflammatory diseases, but not comparable with the systemic inflammation in IBD.

CBF values can reveal changes in tissue perfusion and are an indication for cerebral metabolism changes.[71] In the present study, significant higher CBF values were found in the patient population. Increased CBF is thought to be a compensatory mechanism in response to ischemia or injury, which could be the case in the CD patients due to inflammation.[72-73] Our findings are in line with the results of Wang et al. who described in their cohort that SLE patients had higher CBF values compared with healthy controls.[74]

The volumetric results in this study extend on earlier findings in IBD patients. The reduced GM content of the superior frontal gyrus demonstrated in this study is in agreement with results presented by Agostini et al.[75] The superior frontal gyrus is involved the self-awareness, and important in processing information.[76-77] It has been suggested that the observed decrease in local GM volume could have many causes, including a decrease in cell size, neural or glial cell apoptosis or changes in blood flow.[73] It is not clear whether this local volume reduction is directly linked to systemic inflammation, but it may represent the anatomical substrate for the development of cognitive and emotional disturbances.[75,78] Similar significant positive correlations have been found between the GM volume in aging and measures of short-term memory.[79]

Besides MRI findings, neuropsychological findings were assessed in this study. Previously, no evidence has been obtained on the association of the intrinsic disease process and cognitive dysfunction in IBD patients. It is probable that concurrent mood disorders, in particular depression, affect the cognitive performance of IBD patients in memory and executive functioning tasks.[56] This may be the case in the current cohort, since depressive symptoms were correlated with reduced neuropsychological scores in the three different domains: cognitive func-

tioning, memory and executive functioning. However, Berrill et al. suggested that intellectual deficits existed in IBD patients compared to controls and remained significant after the correction for educational level and mood disorders.[80]

Previous studies have shown a link between systemic inflammation and reduced brain volumes, possibly resulting in cognitive deficits. Zonis et al. suggested that chronic intestinal inflammation alters hippocampal neurogenesis and thus might underlie the behavioural manifestations in patients with IBD.[81] In another study, SLE patients with cognitive deficits appeared to have reduced temporal lobe structures (hippocampus and amgydala) compared to SLE patients without cognitive deficits.[82] In the present study, we did not find these correlations.

Some limitations of this study need to be revealed. Although this study is an exploratory study, the population size was limited. In this pilot study we have compared the most extreme cases; quiescent CD patients with fatigue versus healthy controls without fatigue. In this design, we have found significant differences between the groups and now further research is required. In addition, the significant difference in the fatigue score between patients and controls is not a finding of the study, but part of the design. As a consequence, it cannot be definitely concluded whether the differences in MRI measures are caused by CD per se or represent only patients with combined CD and fatigue. However, fatigue is a subjective measurement and was evaluated as such. It is hard to draw major conclusions from these questionnaires, since some healthy controls reported a high fatigue score as well due to other circumstances than IBD. In some MRI analyses, subjects got excluded due to the quality of the data. MRS data with high Cramer-Rao lower bounds, suggesting unreliable metabolite quantification, were excluded from data analysis. This could have been influenced by the patients' motion or bad shimming.

In conclusion, our findings support the hypothesis that systemic inflammation influences the brain and effects cognitive functioning and mood. This is a first step in the gathering of data and understanding of brain involvement in CD patients. This study implies that for a health professional, it is important to focus in CD patients not only on symptoms related to the gastrointestinal tract, but also on the effects of inflammation on the brain. Understanding these affects in CD patients may help health professionals to set up interventions to maintain CD remission by the use of medication and to improve mood status and QoL by e.g. psychosocial interventions.

REFERENCES

1. Baumgart DC, Sandborn WJ. Crohn's Disease. Lancet 2012;380:1590-1605.
2. Salem M, Ammitzboell M, Nys K, et al. ATG16L1: a multifunctional susceptibility factor in Crohn disease. Autophagy 2015;11(4):585-94.
3. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, et al. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. Inflamm Bowel Dis 2011;17:1564-72.
4. Romberg-Camps MJ, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands; the IBD-South Limburg cohort. Inflamm Bowel Dis 2010;16:2137147.
5. Høivik ML, Bernklev T, Solberg IC, et al. Patients with Crohn's disease experience reduced general health and vitality in the chronic stage: ten-year results from the IBSEN study. J Crohns Colitis 2010;6:441-53.
6. Chen ML, Sundrud MS. Cytokine and T-cell subsets in inflammatory bowel diseases. Inflamm Bowel Dis 2016;22(5):1157-67.
7. Loddo I, Romano C. Inflammatory bowel disease: genetics, epigenetics and pathogenesis. Front Immunol 2015;6:551.
8. Nadeau S, Rivest S. Effects of circulating tumor necrosis factor on the neuronal activity and expression of the genes encoding the tumor necrosis factor receptors (p55 and p75) in the rat brain: a view from the blood-brain barrier. Neuroscience 1999;93(4):1449-64.
9. Hagel AF, de Rossi T, Konturek PC, et al. Plasma histamine and tumour necrosis factor-alpha levels in Crohn's disease and ulcerative colitis at various stages of disease. J Physiol Pharmacol 2015;66(4):549-56.
10. Kader HA, Tchernev VT, Satyaraj E, et al. Protein microarray analysis of disease activity in pediatric inflammatory bowel disease demonstrates elevated serum PLGF, IL-7, TGF-β1, and IL-12p40 levels in Crohn's disease and ulcerative colitis patients in remission versus active disease. Am J Gastroenterol 2005;100:414-23.
11. Emmer BJ, van der Bijl AE, Huizinga TW, et al. Brain involvement in rheumatoid arthritis: a magnetic resonance spectroscopy study. Arthritis Rheum 2009;60:3190-95.
12. O'Callaghan JP, Sriram K, Miller DB. Defining "neuroinflammation". Ann N Y Acad Sci 2008;1139:318-30.
13. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor α signalling during peripheral organ inflammation. J Neurosci 2009;29(7):2089-2102.
14. Hollingworth W, Todd CJ, Bell MI, et al. The diagnostic and therapeutic impact of MRI: an observational multi-centre study. Clin Radiol 2000;55:825-31.
15. Smith, SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–55.
16. Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21-36.
17. Grossman RI, Gomori JM, Ramer KN, et al. Magnetization transfer: theory and clinical applications in neuroradiology. Radiographics 1994;14:279-90.
18. Rosen Y, Lenkinski RE. Recent advances in magnetic resonance neurospectroscopy. Neurotherapeutics 2007;4:330-45.

19. Detre JA, Leigh JS, Williams DS, et al. Perfusion imaging. Magn Reson Med 1992;23(1):37-45.
20. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. Radiology 2000;217:331-45.
21. Schmidt R, Schmid H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 2002;52:168-74.
22. Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology 2009;73:768-74.
23. Moreno B, Jukes JP, Vergara-Irigaray N, et al. Systemic inflammation induces axon injury during brain inflammation. Ann Neurol 2011;70:932-42.
24. Mulak A, Bonaz B. Brain-gut microbiota axis in Parkinson's disease. World J Gastroenterol 2015;21(37):10609-20.
25. Puri BK, Counsell SJ, Zaman R, et al. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. Acta Psychiatr Scand 2002;106:224-26.
26. Hamed SA, Selim ZI, Elattar AM, et al. Assessment of biocorrelates for brain involvement in female patients with rheumatoid arthritis. Clin Rheumatol 2012;31:123-32.
27. Soares DP, Law M. Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. Clin Radiol 2009;64:12-21.
28. Cutolo M, Nobili F, Sulli A, et al. Evidence of cerebral hypoperfusion in scleroderma patients. Rheumatology 2000;39:1366-73.
29. Emmer BJ, Steens SC, Steup-Beekman GM, et al. Detection of change in CNS involvement in neuropsychiatric SLE: a magnetization transfer study. J Magn Reson Imaging 2006;24(4):812-16.
30. Luyendijk J, Steens SC, Ouwendijk WJ, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011;63(3):722-32.
31. Emmer BJ, Veer IM, Steup-Beekman GM, et al. Tract-based spatial statistics on diffusion tensor imaging in systemic lupus erythematosus reveals localized involvement of white matter tracts. Arthritis Rheum 2010;62(12):3716-21.
32. Wang PI, Cagnoli PC, McCune WJ, et al. Perfusion-weighted MR imaging in cerebral lupus erythematosus. Acad Radiol 2012;19:965-70.
33. Puri BK, Counsell SJ, Zaman R, et al. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. Acta Psychiatr Scand 2002;106(3):224-26.
34. Chaudhuri A, Condon BR, Gow JW, et al. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. Neuroreport 2003;14(2):225-28.
35. Puri BK, Holmes J, Hamilton G. Eicosapentaenoic acid-rich essential fatty acid supplementation in chronic fatigue syndrome associated with symptom remission and structural brain changes. Int J Clin Prac 2004;58(3):297-99.
36. Sandu AL, Staff RT, McNeil CJ, et al. Structural brain complexity and cognitive decline in late life – a longitudinal study in the Aberdeen 1936 Birth Cohort. Neuroimage 2014;100:558-63.
37. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.
38. Smets EMA, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosomat Res 1995;39:315-25.
39. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147-53.
40. Zhang Y, Brady M, Smith SM. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imag 2001;20(1):45-47.
41. Patenaude B, Smirth SM, Kennedy DN, et al. A Bayesian model of shap and appearance for

subcortical brain segmentation. Neuroimage 2011;56:907-22.
42. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23:S208-19.
43. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5(2):143-56.
44. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30(6):672-79.
45. Choi JK, Dedeoglu A, Jenkins BG. Applications of MRS to mouse models of neurodegenerative illness. NMR Biomed 2007;20(3):216-37.
46. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med 2015;73(1):102-16.
47. Enkinson M, Bannister P, Brady JM, et al. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17(2):825-41.
48. Leemans A, Jeurisson B, Sijbers J, et al. Explore DTI: a graphical toolbox for processing, analyzing and visualizing diffusion MR data. Annual meeting of Intl Soc Mag Res Med Hawaii, USA 2009, p 3537.
49. Smith SMJ, Jenkinson M, Johansen-Berg, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31(4):1497-505.
50. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
51. Wechsler D. Wechsler Adult Intelligence Scale, Revised. The Psychological Corporation 1981.
52. Wechsler D. Wechsler Memory Scale, Revised. The Pyschological Corporation 1987.
53. Pendleton MG, Heaton RK, Lehman RA, et al. Diagnostic utility of the Thurstone Word Fluency Test in neuropsychological evaluations. J Clin Neuropsychol 1982;4:307-17.
54. Golden CJ. Identification of brain disorders by the Stroop Color and Word-Test. J Clin Psychol 1976;32:654-58.
55. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press 1993.
56. Castaneda AE, Tuulio-Henriksson A, Aronen ET, et al. Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease. World J Gastroenterol 2013;19:1611-17.
57. Brennan C, Worrall-Davies A, McMillan D, et al. The Hospital Anxiety and Depression Scale: A diagnostic meta-analysis of case-finding ability. J Psychosomat Res 2010;69:371-78.
58. Ware JE, Sherbourne CA. The MOS 36-item Short-Form health survey (SF-36). Conceptual framework and item selection. Med Care 1992;30:473-83.
59. Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. Behav Brain Res 2003;140(1-2):1-47.
60. Bianchin M, Da Silva RC, Schmitz PK, et al. Memory of inhibitory avoidance in the rat is regulated by glutamate metabotropic receptors in the hippocampus. Behav Pharmacol 1994;5:356-59.
61. Antuono PG, Jones JL, Wang Y, et al. Decreased glutamate + glutamine in Alzheimer's disease detected in vivo with H-MRS at 0.5T. Neurology 2001;56(6):737-42.
62. Gunnersen D, Haley B. Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker. Proc Natl Acad Sci USA 1992;89(24):11949-53.
63. Hasler G, van der Veen JW, Tumonis T, et al. Reduced prefrontal glutamate/glutamine and gam-

ma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 2007;64(2):193-200.
64. Bernstein HG, Meyer-Lotz G, Dobrowolny H, et al. Reduced density of glutamine synthetase immunoreactive astrocytes in different cortical areas in major depression but not in bipolar I disorder. Front Cell Neurosci 2015;10:273.
65. Brooks WM, Jung RE, Ford CC, et al. Relationship between neurometabolite derangement and neurocognitive dysfunction in systemic lupus erythematosus. J Rheumatol 1999;26(1):81-85.
66. Brenner RE, Munro PM, Williams SC, et al. The proton NMR spectrum in acute EAE: the significance of the change in the Cho:Cr ratio. Magn Reson Med 1993;29(6):737-45.
67. Bitsch A, Bruhn H, Vougioukas V, et al. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. AJNR Am J Neuroradiol 1995;20(9):1619-27.
68. Bjartmar C, Kidd G, Mörk S, et al. Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. Ann Neurol 2000;48(6):893-901.
69. Demougeot C, Garnier P, Mossiat C, et al. N-Acetylaspartate, a marker of both cellular dysfunction and neuronal loss: its relevance to studies of acute brain injury. J Neurochem 2001;77(2):408-15.
70. Adalsteinsson E, Sullivan EV, Kleinhans N, et al. Longitudinal decline of the neuronal marker N-acetyl aspartate in Alzheimer's disease. Lancet 2000;355(9216):1696-97.
71. Wang Z, Das SR, Xie SX, et al. Arterial spin labelled MRI in prodromal Alzheimer's disease: A multi-site study. Neuroimage Clin 2013;30:630-36.
72. Smith M. Perioperative uses of transcranial perfusion monitoring. Neurosurgery clinics of North America 2008;19:489-502.
73. Alsop DC, Casement M, de Bazelaire C, et al. Hippocampal hyperperfusion in Alzheimer's disease. Neuroimage 2008;42(4):1267-74.
74. Wang PI, Cagnoli PC, McCune WJ, et al. Perfusion-weighted MR imaging in cerebral lupus erythematosus. Acad Radiol 2012;19:965-70.
75. Agostini A, Benuzzi F, Filippini N, et al. New insights into the brain involvement in patients with Crohn's Disease: a voxel-based morphometry study. Neurogasterol Motil 2013;25:147-e82.
76. Goldberg I, Harel M, Malach R. When the brain loses its self: prefrontal inactivation during sensorimotor processing. Neuron 2006;50(2):329-39.
77. Miller AK, Alston RL, Corsellis JA. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. Neuropathol Appl Neurobiol 1980;6(2):119-32.
78. Zikou AK, Kosmidou M, Astrakas LG, et al. Brain involvement in patients with inflammatory bowel disease: a voxel-based morphometry and diffusion tensor imaging study. Eur Radiol 2014;24:2499-2506.
79. Taki Y, Kinomura S, Sato K, et al. Correlation between grey/white matter volume and cognition in healthy elderly people. Brain and cognition 2011;75(2):170-76.
80. Berrill JW, Gallacher J, Hood K, et al. An observational study of cognitive function in patients with irritable bowel syndrome and inflammatory bowel disease. Neurogastroenterol Motil 2013;25:918-e704.
81. Zonis S, Pechnick RN, Ljubimov VA, et al. Chronic intestinal inflammation alters hippocampal neurogenesis. J Neuroinflammation 2015;12;65.
82. Zimmermann N, Corrêa DG, Kubo TA, et al. Global cognitive impairment in systemic lupus erythematosus patients: A structural MRI study. Clin Neuroradiol 2017;27(1):23-29.

TABLES AND FIGURES

Table 1. Demographic characteristics.

	CD patients (n=20)	Controls (n=17)	P-value
Age (years) at inclusion, mean ± SD	30.1 ± 6.2	28.5 ± 6.7	0.320
Female, n (%)	17 (85.0)	13 (76.5)	0.523
HBI score, mean ± SD #	2.2 ± 1.1	-	-
Age of IBD onset (years), mean ± SD	21.4 ± 5.7	-	-
IBD disease duration (years), mean ± SD	8.8 ± 7.2	-	-
Smoker, n (%)	11 (55.0)	4 (23.5)	0.416
VAS, mean ± SD	7.4 ± 1.3	3.4 ± 2.3	<0.001
MFI, mean ± SD	66.1 ± 13.3	36.4 ± 10.3	<0.001
General Fatigue	16.4 ± 2.8	8.9 ± 3.3	<0.001
Physical Fatigue	14.4 ± 3.0	6.2 ± 2.2	<0.001
Mental Fatigue	12.8 ± 4.1	7.2 ± 2.9	<0.001
Reduced Activity	10.7 ± 3.5	6.9 ± 2.7	<0.001
Reduced Motivation	12.0 ± 3.6	7.1 ± 2.7	<0.001
Education level, n (%)			0.001
Low[a]	4 (20)	-	
Intermediate[b]	10 (50)	2 (11.8)	
High[c]	6 (30)	15 (88.2)	
Montreal Classification			
Location CD, n (%)			
L1 ileal	3 (15.0)	-	-
L2 colonic	2 (10.0)	-	-
L3 ileocolonic	15 (75.0)	-	-
L4 upper	-	-	-
L1-3+L4	-	-	-
Behaviour CD, n (%)			
B1 non-stricturing/penetrating	15 (75.0)	-	-
B2 stricturing	3 (15.0)	-	-
B3 penetrating	2 (10.0)	-	-
+ Perianal disease	3 (15.0)	-	-
Medication use, n (%)			
Immunosuppressive drugs (Aza/6MP)	12 (60.0)	-	-
None	8 (40.0)	-	-

HBI missing of 1 CD patient. HBI: Harvey Bradshaw Index, VAS: Visual Analogue Scale, MFI: Multidimensional Fatigue Index.
[a] Low: primary education (elementary school) and lower secondary education (preparatory secondary education); [b] Intermediate: higher secondary education (higher general continued education, pre-university secondary education) and postsecondary education (intermediate vocational education); [c] High: tertiary education (higher professional education, university). *To correct for multiple testing, the level of significance was set at $p < 0.01$ for the MFI score.*

Table 2. Group mean subcortical structure volumes as percentage of the total brain volume in CD patients and controls.

	CD patients (n=20)	Controls (n=17)	P-value
Left Accumbens	0.04 ± 0.01	0.04 ± 0.01	0.56
Left Amygdala	0.09 ± 0.01	0.09 ± 0.01	0.61
Left Caudate	0.24 ± 0.02	0.24 ± 0.02	0.94
Left Hippocampus	0.27 ± 0.02	0.27 ± 0.03	0.94
Left Pallidus	0.13 ± 0.01	0.12 ± 0.01	0.32
Left Putamen	0.33 ± 0.02	0.32 ± 0.03	0.24
Left Thalamus	0.54 ± 0.02	0.54 ± 0.03	0.94
Right Accumbens	0.04 ± 0.00	0.03 ± 0.01	0.08
Right Amygdala	0.08 ± 0.01	0.09 ± 0.01	0.08
Right Caudate	0.25 ± 0.03	0.25 ± 0.02	0.76
Right Hippocampus	0.26 ± 0.02	0.27 ± 0.03	0.22
Right Pallidus	0.12 ± 0.01	0.13 ± 0.01	0.30
Right Putamen	0.31 ±0.08	0.32 ± 0.02	0.56
Right Thalamus	0.53 ± 0.02	0.52 ± 0.03	0.48

Mean subcortical volume in % ± SD.

Table 3. Mean metabolite ratio to total Creatine.

	CD patients (n=9)	Controls (n=9)	P-value
Ratio Glu:tCr	0.76 ± 0.12	0.84 ± 0.10	0.19
Ratio Cho:tCr	0.29 ± 0.02	0.29 ± 0.04	0.81
Ratio Ins:tCr	0.66 ± 0.08	0.70 ± 0.10	0.38
Ratio NAA:tCr	1.31 ± 0.12	1.27 ± 0.09	0.44
Ratio NAA+NAAG:tCr	1.59 ± 0.18	1.56 ± 0.13	0.69
Ratio Glu+Gln:tCr	0.92 ± 0.13	1.10 ± 0.14	0.02

MRS analysis. Mean metabolite ratio to total Creatine (tCr) in mmol ± SD. Glu, Glutamate; Cho, Choline; Ins, Insulin; NAA, N-Acetyl Aspartate; NAAG, N-Acetyl Aspartate Glutamate; Gln, Glutamine.

Table 4. Mental status.

	CD patients (n=20)	Controls (n=17)	P-value
Global cognitive functioning, mean ± SD			
MMSE (total score)	28.9 ± 1.6	29.65 (0.5)	0.87
Memory, mean ± SD			
Verbal			
WMS memory quotient Δ	109.2 ± 10.5	115.7 (8.7)	0.72
Non verbal			
WMS visual reproduction (total score)	11.6 ± 2.7	12.9 (2.2)	0.75
WAIS-R Digit Span forward	5.4 ± 1.0	6.5 (1.3)	0.15
WAIS-R Digit Span backward	4.5 ± 1.0	5.2 (0.9)	0.15
Executive functioning, mean ± SD			
WFT †			
No. of good answers	42.7 ± 7.8	48.2 (9.8)	0.29
No. of perseverative errors	0.28 ± 0.5	0.47 (0.8)	0.58
Stroop Color-Word test, mean ± SD			
Stroop 1 time (sec)	43.9 ± 7.2	39.2 (8.6)	0.41
Stroop 1 no. of errors	0.2 ± 0.4	0.1 (0.3)	0.98
Stroop 2 time (sec)	56.6 ± 8.3	53.8 (6.9)	0.62
Stroop 2 no. of errors	0.3 ± 0.8	0 (0.0)	0.21
Stroop 3 time (sec)	88.3 ± 14.7	76.6 (8.8)	0.22
Stroop 3 no. of errors	0.6 ± 1.5	0.13 (0.3)	0.20
Stroop interference index	50.1 ± 7.8	56.1 (5.5)	0.06
TMT, mean ± SD			
Part A time (sec)	30.3 ± 11.8	22.1 (8.5)	0.08
Part A no. of errors	0.1 ± 0.2	0.1 (0.2)	0.56
Part B time (sec)	61.8 ± 29.2	50.1 (17.4)	0.72
Part B no. of errors	0.1 ± 0.2	0.2 (0.5)	0.41
WAIS-R Digit Symbol, mean ± SD§			
Total score	59.7 ± 8.4	71.0 (6.2)	0.06
No. of errors	0 ± 0.0	0.1 (0.3)	0.63
Digit cancellation test, mean ± SDψ			
Total score	436.2 ± 88.1	498.6 (82.9)	0.16
No. of good answers (%)	57.3 ± 29.5	78.9 (20.9)	0.16
HADS, mean ± SD	13.1 ± 7.3	4.8 (2.9)	<0.001
Anxiety	7.5 ± 3.8	3.7 (2.7)	0.002
Depression	6.1 ± 4.0	0.9 (1.1)	<0.001
SF-36, mean ± SD			
Physical functioning	72.9 ± 20.2	96.6 ± 3.4	<0.001
Social functioning	52.0 ± 29.0	90.7 ± 9.8	<0.001
Role physical problem	71.3 ± 37.4	2.9 ± 8.3	<0.001
Role emotional problem	40.4 ± 46.1	2.0 ± 8.1	0.002
Bodily pain	35.3 ± 20.7	5.6 ± 12.6	<0.001
General health perception	65.8 ± 18.8	82.0 ± 15.2	<0.001
Mental health	63.6 ± 16.0	80.4 ± 10.9	0.001
Vitality	30.1 ±18.3	72.9 ± 14.3	<0.001

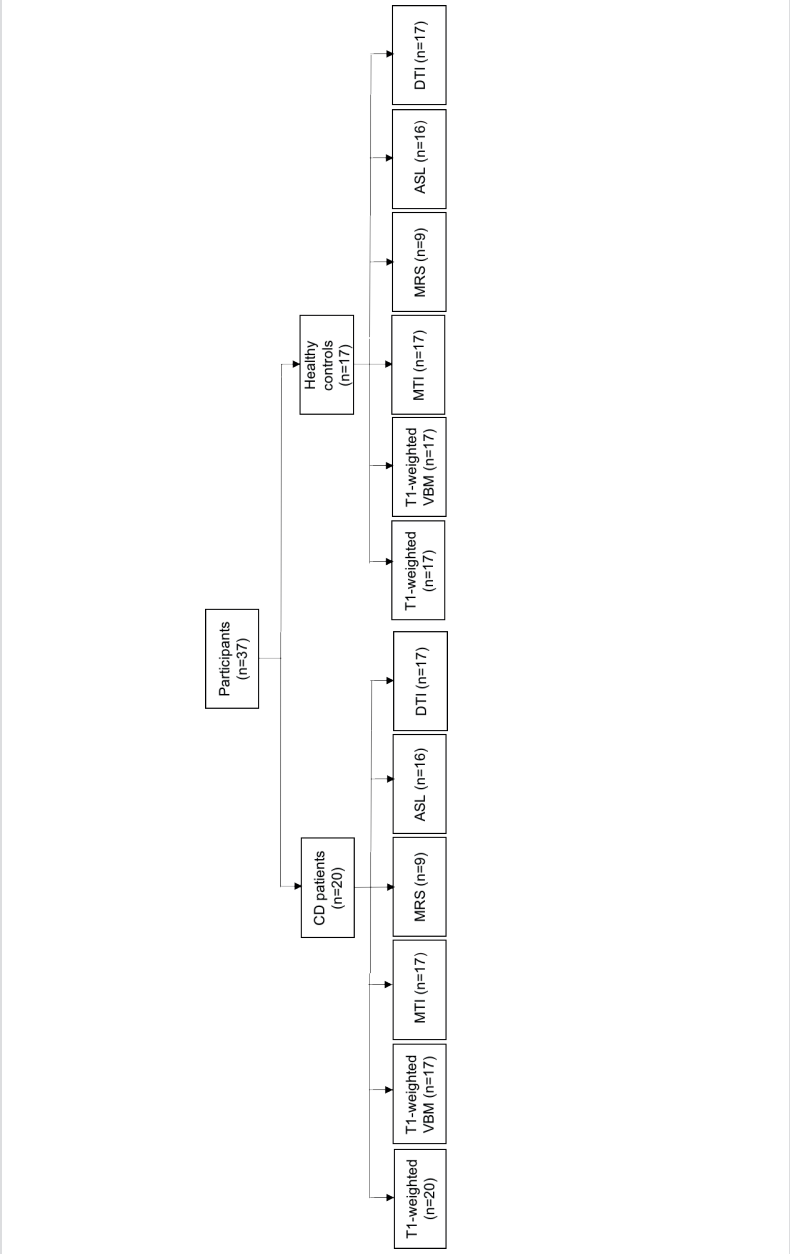
MMSE: Mini Mental State Examination; WMS: Wechsler Memory Scale; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WFT: Word Fluency Test; TMT: Trial Making test.
† Missing in 2 CD patients, § Missing 1 CD patient and 1 healthy control, Δ Missing in 2 healthy controls, ψ Missing in 5 patients and 3 healthy controls. To correct for multiple testing, the level of significance was set at p<0.006 for the SF-36 score.

Table 5. Z-scores of the different domains of cognitive functioning.

	CD patients (n=20)	Controls (n=17)	P-value
Global cognitive functioning, mean ± SD	28.9 ± 1.6	29.7 ± 0.5	0.87
Memory, mean ± SD	1.1 ± 2.9	1.3 ± 2.3	0.007
Executive functioning, mean ± SD	2.5 ± 7.7	2.9 ± 4.2	0.02

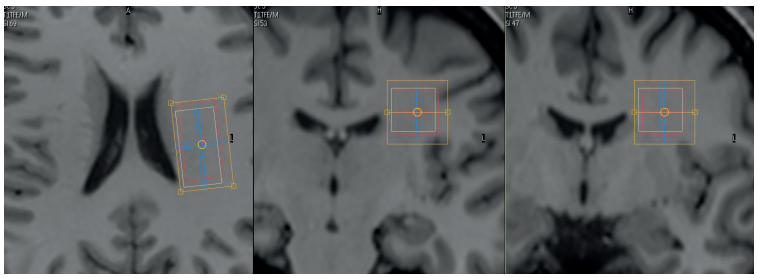
The global cognitive functioning domain includes the MMSE. The memory domain includes the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Wechsler Memory Scale (WMS). The executive functioning domain includes the Word Fluency Test (WFT), Stroop Color Word Test (SCWT) and the Trial Making test (TMT).

Figure 1. Flowchart of included participants in the MRI analyses.



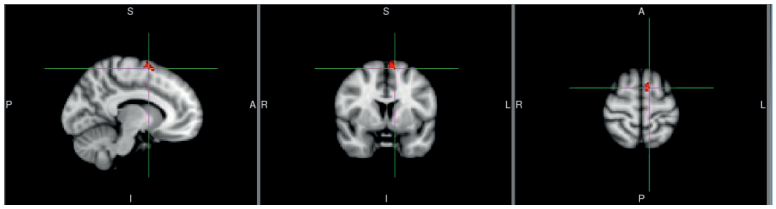
T1-weighted VBM: T1-weighted Voxel Based Morphometry, MTI: Magnetization Transfer Images, MRS: Magnetic Resonance Spectroscopy, ASL: Arterial Spin Labelling, DTI: Diffusion Tensor Imaging.

Figure 2. Planning of the ^{1}H-MRS volume of interest (VOI) in the left centrum semi-ovale.



Seen on axial (left) and on the coronal (right) T1-weighted image slices. The effective VOI set at the tNAA frequency is shown (red rectangle) together with the shimming volume (yellow rectangle).

Figure 3. FSL VBM analysis.



Voxel based morphometry (VBM) results shown on MNI152 standard space. The red colour indicates the voxels with significantly reduced grey matter volume in CD patients compared with healthy controls (with a p-value <0.05, corrected for multiple comparison). The red voxels correspond to the left superior frontal gyrus.

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.

REFERENCES

1. Zhang Y, Li Y. Inflammatory bowel disease: Pathogenesis. World J Gastroenterol 2014;20(1):91-99.
2. Card TR, Langan SM, Chu TP. Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported. Dig Dis Sci 2016;61(9):2619-26.
3. De Wilde K, Debusschere K, Beeckman S, et al. Integrating the pathogenesis of spondyloarthritis: gut and joint united? Curr Opin Rheumatol 2015;27(2):189-96.
4. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, et al. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. Inflamm Bowel Dis 2011;17:1564-72.
5. Romberg-Camps MJ, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands; the IBD-South Limburg cohort. Inflamm Bowel Dis 2010;16:2137-47.
6. Emmer BJ, van der Bijl AE, Huizinga TW, et al. Brain involvement in rheumatoid arthritis: a magnetic resonance spectroscopy study. Arthritis Rheum 2009;60:3190-3195.
7. Hamed SA, Selim ZI, Elattar AM, et al. Assessment of biocorrelates for brain involvement in female patients with rheumatoid arthritis. Clin Rheumatol 2012;31:123-32.
8. Luyendijk J, Steens SC, Ouwendijk WJ, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011;63(3):722-32.
9. Emmer BJ, Veer IM, Steup-Beekman GM, et al. Tract-based spatial statistics on diffusion tensor imaging in systemic lupus erythematosus reveals localized involvement of white matter tracts. Arthritis Rheum 2010;62(12):3716-21.
10. Karreman MC, Luime JJ, Hazes JMW, et al. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis 2017;11(5):631-42.
11. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:2217-37.
12. 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.
13. 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.
14. 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;27:361-68.
15. Van Erp SJ, Brakenhoff LK, van Gaalen FA, et al. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2016;10(2):166-75.
16. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut 1998;42:387-91.
17. 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.

18. Westlund KN, Zhang L, Ma F, et al. Chronic Inflammation and Pain in a TNFR (p55/p75-/-) Dual Deficient Murine Model. Transl Res 2012;160(1):84–94.
19. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gatroenterol Hepatol 2015;12(9):537-45.
20. den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis 2002;61(4):311-18.
21. Gaffen SL, Jain R, Garg AV, et al. The IL-23 IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 2004;14:585–600.
22. Orchard TR, Thiyagaraja S, Welsh KI, et al. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. Gastroenterology 2000;118(2):274-78.
23. Orchard TR, Dhar A, Simmons JD, et al. MHC class I chain-like gene A (MICA) and its associations with inflammatory bowel disease and peripheral arthropathy. Clin Exp Immunol 2001;126(3):437-40.
24. Wallis D, Asaduzzaman A, Weisman M, et al. Elevated serum anti-flagellin antibodies implicate subclinical bowel inflammation in ankylosing spondylitis: an observational study. Arthritis Res Ther 2013;15(5):R166.
25. De Vries M, van der Horst-Bruinsma I, van Hoogstraten I, et al. pANCA, ASCA, and OmpC antibodies in patients with ankylosing spondylitis without inflammatory bowel disease. J Rheumatol 2010;37(11):2340-44.
26. Matzkies FG, Targan SR, Berel D, et al. Markers of intestinal inflammation in patients with ankylosing spondylitis: a pilot study. Arthritis Res Ther 2012;14(6):R261.
27. Thia KT, Loftus EV Jr, Sandborn WJ, et al. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 2008;103:3167-82.
28. Vidotto JP, Pereira LA, Braga AL, et al. Atmospheric pollution: influence on hospital admissions in paediatric rheumatic diseases. Lupus 2012;21(5):526-33.
29. Zeboulon-Ktorza N, Boelle PY, Nahal RS, et al. Influence of Environmental Factors on Disease Activity in Spondyloarthritis: A Prospective Cohort Study. J Rheumatol 2013;40(4):469-75.
30. Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Ther 1999;13:1403-11.
31. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. Am J Gastroenterol 2012;107:1399-1406.
32. Dougados M, Demattei C, van den Berg R, et al. Rate and Predisposing Factors for Sacroiliac Joint Radiographic Progression After a Two-Year Follow-up Period in Recent-Onset Spondyloarthritis. Arthritis Rheumatol 2016;68(8):1904-13.
33. Cantorna MT, Mahon BD. D-hormone and the immune system. J Rheumatol 2005;76:11-20.
34. Froicu M, Cantorna MT. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. BMC Immunol 2007;8:5.
35. Hmamouchi I, Paternotte S, Molto A, et al. Vitamin D, disease activity and comorbidities in early spondyloarthritis. Clin Exp Rheumatol 2016;34(3):396-403.
36. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol 2009;104:1298-1313.
37. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 2008;57:1386-92.

38. Van Erp SJ, Verheul MK, Levarht EW, et al. Short article: Absence of serological rheumatoid arthritis biomarkers in inflammatory bowel disease patients with arthropathies. Eur J Gastroenterol Hepatol 2017;29(3):345-48.
39. Van der Have M, Minderhoud IM, Kaptein AA, et al. Substantial impact of illness perceptions on quality of life in patients with Crohn's disease. J Crohns Colitis 2012;7:292-301.
40. Jordan C, Sin J, Fear NT, et al. A systematic review of the psychological correlates of adjustment outcomes in adults with inflammatory bowel disease. Clin Psychol Rev 2016;47:28-40.
41. 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(3):276-83.
42. Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R). Psychol Health 2002;17:1-16.
43. Maes S, Leventhal H, de Ridder DTD. Coping with chronic diseases. Zeidner M, Endler NS, eds. Handbook of coping. New York: Wiley 1996:221-51.
44. Leventhal H, Brissette I, Leventhal, EA. The common-sense model of self-regulation of health and illness. In L. D. Cameron & H. Leventhal (Eds.) The self-regulation of health and illness behaviour. London: Routledge; 2003:42-65.
45. Van Erp SJ, Brakenhoff LK, Vollmann M, et al. Illness perceptions and outcomes in patients with inflammatory bowel disease: is coping a mediator? Int J Behav Med 2017;24(2):205-14.
46. Dorrian A, Dempster M, Adair P. Adjustment to inflammatory bowel disease: the relative influence of illness perceptions and coping. Inflamm Bowel Dis 2009;15:47-55.
47. Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to inflammatory bowel disease. Inflamm Bowel Dis 2010;16:1685-95.
48. Mikocka-Walus A, Bampton P, Hetzel D, et al. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomized controlled trial. BMC Gastroenterol 2015;15:54.
49. Mussell M, Bocker U, Nagel N, et al. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. Scand J Gasteroenterol 2003;38(7):755-62.
50. Knowles SR, Monshat K, Castle DJ, et al. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. Inflamm Bowel Dis 2013;19:2704–15.
51. Hauser G, Pletikosic S, Tkalcic M, et al. Cognitive behavioral approach to understanding irritable bowel syndrome. World J Gastroenterol 2014;20:6744–58.
52. Keefer L, Doerfler B, Artz C, et al. Optimizing management of Crohn's disease within a project management framework: results of a pilot study. Inflamm Bowel Dis 2012;18:254–60.
53. Lykouras D, Karkoulias K, Triantos C. Physical exercise in patients with inflammatory bowel disease. J Crohns Colitis 2017;11(8):1024.
54. Gåfvels C, Hägerström M, Rane K, Wajngot A, Wändell PE. Coping strategies among patients newly diagnosed with diabetes or rheumatoid arthritis at baseline and after 24 months. J Health Psychol 2016.
55. Van Erp S, Ercan E, Breedveld P, et al. Cerebral magnetic resonance imaging in quiescent Crohn's disease patients with fatigue. World J Gastroenterol 2017;23(6):1018-29.
56. Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. Behav Brain Res 2003;140(1-2):1-47.

57. Antuono PG, Jones JL, Wang Y, et al. Decreased glutamate + glutamine in Alzheimer's disease detected in vivo with H-MRS at 0.5T. Neurology 2001;56(6):737-42.
58. Smith M. Perioperative uses of transcranial perfusion monitoring. Neurosurgery clinics of North America 2008;19:489-502.
59. Alsop DC, Casement M, de Bazelaire C, et al. Hippocampal hyperperfusion in Alzheimer's disease. Neuroimage 2008;42(4):1267-74.
60. Wang PI, Cagnoli PC, McCune WJ, et al. Perfusion-weighted MR imaging in cerebral lupus erythematosus. Acad Radiol 2012;19:965-70.
61. Zonis S, Pechnick RN, Ljubimov VA, et al. Chronic intestinal inflammation alters hippocampal neurogenesis. J Neuroinflammation 2015;12;65.
62. Zimmermann N, Corrêa DG, Kubo TA, et al. Global cognitive impairment in systemic lupus erythematosus patients: A structural MRI study. Clin Neuroradiol 2017;27(1):23-29.
63. De Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000;27:2860-65.
64. 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;13(6):1042-50.
65. Barreiro-de-Acosta M, Lorenzo A, Domínguez-Muñoz JE et al. Efficacy of adalimumab for the treatment of extraintestinal manifestations of Crohn's disease. Rev Esp Enferm Dig 2012;104(9):468-72.
66. Severs M, van Erp SJ, van der Valk ME, et al. Smoking is Associated With Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis 2016;10(4):455-61.
67. Brakenhoff LKPM, van der Heijde D, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. Gut 2011;60:1426-35.
68. Jordan JL, Holden MA, Mason EE, et al., Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2010;1:CD005956
69. Ferwerda M, van Beugen S, van Middendorp H, et al. A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial. Pain 2017;158(5):868-78.
70. Cuijpers P, van Straten A, Andersson G. Internet-administered cognitive-behavioural therapy for health problems: a systemic review. J Behav Med 2008;31(2):169–77.
71. Ferwerda M, van Beugen S, van Burik A, et al. What patients think about e-health: patients' perspective on internet-based cognitive behavioral treatment for patients with rheumatoid arthritis and psoriasis. Clin Rheumatol 2013;32(6):869-73.
72. Aguas Peris M, Del Hoyo J, Bebia P et al. Telemedicine in inflammatory bowel disease: opportunities and approaches. Inflamm Bowel Dis 2015;21(2):392-99.
73. Marin-Jimenez I, Montoya MG, Panadero A, et al. Management of the psychological impact of inflammatory bowel disease: perspective of doctors and patients – The ENMENTE Project. Inflamm Bowel Dis 2017;23:1492-98.
74. Papamichael K, Tsirogianni A, Papasteriades C, et al. Low prevalence of antibodies to cyclic citrullinated peptide in patients with inflammatory bowel disease regardless of the presence of arthritis. Eur J Gastroenterol Hepatol 2010;22(6):705-9.
75. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis 2010;69:490-94.

76. Shi J, Knevel R, Suwannalai P, et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc Natl Acad of Sci USA 2011;108:17372–77.

CHAPTER 10

Nederlandse samenvatting

ACHTERGROND EN DOEL VAN HET ONDERZOEK

Inflammatoire darmziekten (ook wel: Inflammatory Bowel Disease, IBD) is een chronische ontstekingsziekte van het maag-darmkanaal en omvat de ziekte van Crohn (CD), colitis ulcerosa (CU) en 'indeterminate colitis' (IC). IBD is een auto-immuun ziekte, waarbij antistoffen worden geproduceerd tegen het darmkanaal wat ontsteking in de darm kan induceren. De etiologie van IBD is een samenspel van verschillende factoren waarbij immunologische, genetische, microbiotische, serologische en omgevingsfactoren de belangrijkste zijn. CD kan voorkomen van mond tot anus, maar is voornamelijk gelokaliseerd in het laatste deel van de dunne darm (ileum) of in de dikke darm (colon) en kan alle lagen van de darmwand aantasten. CU is het meest frequent voorkomende type IBD en wordt gekarakteriseerd door een chronische ontsteking van alleen het slijmvlies van de dikke darm. De ontsteking begint in de endeldarm, bij de anus, en kan zich dan verder uitbreiden naar proximaal, zoals de dikke darm. IC wordt bij ongeveer 10% van de IBD-patiënten gediagnosticeerd en omvat de IBD-patiënten waarbij de diagnose CD of CU niet kan worden vastgesteld op basis van aanvullend klinisch onderzoek. IBD wordt met name bij jong volwassenen, tussen de 15 en 35 jaar oud gediagnosticeerd. De incidentie van IBD bedraagt 1 per 1000 individuen in de westerse wereld, welke nog steeds stijgt vanwege onder andere industrialisatie en voeding. Symptomen die voorkomen bij IBD zijn zeer divers en afhankelijk van de lokalisatie van de ziekte. Voorbeelden van klachten zijn onder andere: diarree, buikpijn, bloed en/of slijm bij de ontlasting, afvallen en eventueel misselijkheid en braken. IBD wordt gekenmerkt door perioden van opvlammingen waarbij de symptomen in ernstige mate aanwezig zijn, en perioden van remissie waarbij patiënten vrijwel geen klachten hebben. Het streven is om zo veel mogelijk perioden van remissie te behalen bij de individuele patiënt en op deze manier complicaties op langere termijn en uitbreiding van de ziekte te voorkomen. Veelal kan dit door patiënten in te stellen op (chronische) medicatie en deze medicatie in de tijd indien noodzakelijk aan te passen aan de hand van de klachten.

IBD manifesteert zich niet alleen in de darm, maar mogelijk ook hierbuiten. Extra-intestinale manifestaties (EIM) die voorkomen bij IBD kunnen aandoeningen van de huid, de ogen, lever en gewrichten zijn. In dit proefschrift wordt de nadruk gelegd op IBD gerelateerde gewrichtsklachten, ook wel arthropathieën genoemd, aangezien dit de meest voorkomende EIM is met een prevalentie

van ongeveer 30%. Arthropathieën bij IBD hebben een enorme impact op de kwaliteit van leven, werkproductiviteit en dagelijkse activiteiten. Arthropathieën kunnen worden onderverdeeld in gewrichtsklachten op basis van ontsteking (waaronder Spondyloarthritis; SpA) en gewrichtsklachten zonder dat er sprake is van ontsteking, ook wel artralgie (gewrichtspijn) genoemd. SpA is een verzamelnaam voor een groep reumatische ziekten waarbij de ziekte van Bechterew (Ankyloserende Spondylitis; AS, waarbij de sacro-iliacale (SI) gewrichten en de rug zijn aangedaan) het meest voorkomt. Afhankelijk van de lokalisatie van de gewrichtsklachten kan SpA worden onderverdeeld in perifere en axiale SpA. Bij perifere SpA staan de ontstekingen van de gewrichten en pezen op de voorgrond, terwijl bij axiale SpA vooral ontstekingen in de rug een rol spelen met rugpijn tot gevolg. De prevalentie van SpA varieert van 0.5-1.5%.

Aangezien de Maag-, Darm en Leverarts (MDL-arts) over het algemeen onbekend is met de behandeling van gewrichtsklachten bij IBD willen we aan de hand van dit proefschrift een handvat creëren hoe IBD-patiënten met gewrichtsklachten kunnen worden herkend, op welke manier er onderscheid kan worden gemaakt tussen SpA of artralgie en wanneer IBD patiënten met gewrichtsklachten dienen te worden verwezen naar de reumatoloog voor verder onderzoek en/of behandeling. Bovendien onderzoeken we of de diagnose IBD, maar ook het hebben van arthropathieën bij IBD van invloed is op de ziektepercepties, coping mechanismen, kwaliteit van leven, werkproductiviteit en activiteitenbeperking. Wanneer arthropathieën bij IBD-patiënten in een vroeg stadium worden opgemerkt, kunnen er verschillende medicamenteuze dan wel psychologische interventies worden verricht om de klachten te behandelen.

SAMENVATTING

De pathofysiologische overlap tussen IBD en SpA

In de literatuur worden verschillende studies beschreven over de pathofysiologische overlap tussen IBD en SpA. In **hoofdstuk 2** wordt een overzicht gegeven van deze studies bekend in de literatuur tot december 2016 waarin immunologische, genetische, serologische, microbiotische en omgevingsfactoren van invloed zijn op het ontstaan van zowel IBD als SpA. Tumornecrosefactor (TNF) speelt onder andere een belangrijke rol in het samenspel tussen IBD en SpA waarbij TNF zorgt voor het vrijkomen van verschillende ontstekingsmediatoren (ook wel cytokines genoemd) waardoor een ontstekingsreactie op gang komt.

Normaliter zorgt dit voor de afweer tegen bacteriën en virussen van buitenaf, maar een overmatige productie van TNF kan onverhoopt schade aanrichten en op deze manier zorgen voor een auto-immuun reactie. Anti-TNF therapie blijkt dan ook een effectieve behandeling voor zowel IBD als SpA. Hiernaast draagt interleukine (IL)-23 in combinatie met T-helper (Th) 17 cellen bij aan een overactiviteit van het immuunsysteem wat uiteindelijk zorgt voor chronische ontsteking in het slijmvlies van de darm bij IBD-patiënten dan wel in het synoviale membraan bij patiënten met SpA. Het synoviaal membraan produceert vocht en zorgt er voor dat het gewricht soepel kan bewegen. In een vroeg stadium raakt dit membraan ontstoken en wordt het dikker waardoor pijn en bewegingsbeperking ontstaat. Naast immunologische reacties worden ook genetische factoren beschreven die bijdragen aan de pathofysiologische overlap tussen IBD en SpA. Er is onder andere aangetoond in de literatuur dat individuen bij wie het humaan leukocytenantigeen (HLA)-B27 aanwezig is in het bloed, een verhoogd risico hebben op het ontwikkelen van zowel IBD als SpA. Met name AS, zoals eerder beschreven de meest voorkomende vorm van SpA, is geassocieerd met de aanwezigheid van HLA-B27. Naast HLA-B27 worden andere genetische factoren in dit proefschrift genoemd die mogelijk bijdragen aan de aanwezigheid van arthropathieën bij IBD-patiënten. Desondanks zijn ook tegenstrijdige conclusies in de literatuur over de overlap van genetische factoren tussen IBD en SpA. Zo is er tot op heden nog onduidelijkheid over het *NOD2/CARD15* gen, welke moleculen van de wand van een bacterie detecteert en identificeert, wat leidt tot een (ongecontroleerde) immuunreactie.

Naast genetische factoren zijn er verschillende biomarkers zowel bij IBD- als bij SpA-patiënten in het bloed aan te tonen. Verhoogde waarden van antilichamen tegen de gist Saccharomyces cerevisiae (ASCA), antilichamen tegen het cytoplasma van witte bloedcellen (granulocyten en monocyten: dragen bij aan een immuunreactie) (ANCA), antilichamen tegen het Eschericia coli membraan-eiwit (anti-OmpC) en antilichamen tegen het eiwit flagelline van de bacterie Salmonella typhimunium (anti-CBir1) werden zowel bij IBD als bij SpA-patiënten gedetecteerd. Hiernaast wordt in dit hoofdstuk beschreven dat bij een ontsteking in het lichaam onder andere de witte bloedcellen (neutrofiele granulocyten) een centrale rol spelen in de regulatie van ontstekingsprocessen. Deze witte bloedcellen passeren de darmwand en komen in de ontlasting terecht. Bij het afsterven van deze witte bloedcellen in de ontlasting komt een ontstekingsremmend eiwit vrij, ook wel calprotectine genoemd. Calprotectine kan de groei van bacteriën verhinderen door de lokale concentratie aan cal-

cium- en zink-ionen aan zich te binden. Calcium en zink zijn noodzakelijk voor een optimale bacteriële groei. Calprotectine wordt gebruikt om de ernst van IBD te monitoren. Een recente studie heeft aangetoond dat dit eiwit ook aanwezig is bij SpA-patiënten zonder klinische symptomen van darmontsteking. Hiernaast zijn verschillende omgevingsfactoren geassocieerd met de ontwikkeling van IBD en SpA. IBD en SpA komt met name voor in de westerse wereld en neemt nog steeds toe in aantal. Mogelijke factoren die bijdragen aan deze toename zijn luchtvervuiling, roken, een tekort aan vitamine D en stress.

De classificatie van arthropathieën bij IBD

Zoals eerder vermeld in deze samenvatting kunnen IBD geassocieerde arthropathieën worden onderverdeeld in SpA of artralgie. Het is belangrijk om als MDL-arts dit onderscheid in een vroeg stadium te maken zodat een patiënt bij het vermoeden op SpA kan worden verwezen naar de reumatoloog voor verdere analyse en behandeling. De resultaten uit de **hoofdstukken 3 tot en met 7** zijn gebaseerd op de data uit de JOINT-studie die is gestart in samenwerking met de afdeling reumatologie van het Leids Universitair Medisch Centrum (LUMC). Het cohort omvat 255 IBD-patiënten (155 patiënten met en 100 patienten zonder arthropathieën) die zijn geïncludeerd van juli 2009 tot februari 2010. IBD-patiënten bezochten de polikliniek Maag-, Darm- en Leverziekten van het LUMC en werden verzocht een vragenlijst in te vullen om na te gaan of ze op dat moment, of het afgelopen jaar gewrichtsklachten (hebben) ervaren. De 255 patiënten werden op het moment van inclusie en na 1 jaar gezien op de polikliniek. Op beide momenten werden de voorgeschiedenis, huidige klachten en, indien aanwezig, de EIMs uitgevraagd. Hiernaast werd naast algemeen lichamelijk onderzoek, een reumatologisch onderzoek verricht waarbij werd gelet op zwelling van de gewrichten. Ontstekingswaarden in het bloed (BSE, CRP) werden bepaald en aanvullend beeldvormend onderzoek werd verricht bij de IBD-patiënten met gewrichtsklachten. Alleen de patiënten met verdenking op een gewrichtsontsteking werden verwezen naar de reumatoloog voor verder aanvullend onderzoek. Hiernaast werden alle deelnemers verzocht maandelijks een vragenlijst in te vullen om aan te geven hoeveel klachten ze ervaarden van de IBD en hoeveel gewrichtspijn ze hadden op een schaal van 0 (geen klachten) tot 10 (zeer ernstig). Tevens werden de deelnemers verzocht om zowel op het moment van inclusie als na 1 jaar follow-up vragenlijsten in te vullen om ziektepercepties, coping en de kwaliteit van leven, werkproductiviteit en activiteitenbeperking in te schatten en te evalueren.

In **hoofdstuk 3** worden de gewrichtsklachten geclassificeerd volgens verschillende reumatologische classificatie criteria. Deze classificatie criteria zijn gebaseerd op de verschillende SpA kenmerken: uveitis (ontsteking van de uvea van het oog), dactylitis (ontsteking van een vinger of teen), enthesitis (ontsteking op de overgang waar een pees/ligament aanhecht op bot), inflammatoire rugklachten, psoriasis (huidafwijking), artritis, een gunstig effect van NSAID behandeling op de pijnklachten, verhoogde waarden van het BSE of CRP, aanwezigheid van HLA-B27 in het bloed en een positieve familieanamnese voor SpA. Uiteindelijk wordt in dit hoofdstuk beschreven dat de ASAS criteria voor zowel axiale als perifere SpA het best dagelijks toe te passen zijn in de kliniek. Echter, deze criteria kunnen niet gebruikt worden om de diagnose te stellen. Om na te gaan of de klachten het best verklaard kunnen worden door axiale SpA, kan er gebruikt worden gemaakt van het diagnostisch Berlijn algoritme. Afhankelijk van de bevindingen kan nagegaan worden of axiale SpA waarschijnlijk is. Deze patiënten dienen te worden verwezen naar de reumatoloog voor aanvullend onderzoek en behandeling. Voor het vaststellen van perifere SpA in IBD is het essentieel dat er een zwelling van het gewricht wordt vastgesteld. De reumatoloog zal vaak aanvullend laboratoriumonderzoek of beeldvormend onderzoek verrichten. Uiteindelijk voldeden slechts 12.3% van de IBD-patiënten met gewrichtsklachten aan de ASAS classificatie criteria voor axiale en perifere SpA. De meeste IBD-patiënten met gewrichtsklachten (87.7%) werden geclassificeerd met artralgie. Tevens wordt in het hoofdstuk beschreven dat de meeste patiënten met arthropathieën klachten van de perifere gewrichten ervaarden waarbij vaak meerdere gewrichten waren aangedaan. Factoren die geassocieerd zijn met het hebben van arthropathieën bij IBD zijn een vrouwelijk geslacht, roken en een actieve IBD. Gedurende de 12 maanden follow-up, bleef de hoeveelheid patiënten met gewrichtsklachten redelijk stabiel.

Ziekte percepties, coping mechanismen en ziekte uitkomsten bij IBD-patiënten met en zonder arthropathieën

Kennis over ziektepercepties en coping mechanismen die door IBD-patiënten (met en zonder arthropathieën) worden gehanteerd en de invloed die deze factoren op verschillende ziekte uitkomsten waaronder de kwaliteit van leven, werkproductiviteit en activiteitenbeperking hebben, kunnen leiden tot het ontwikkelen van psychologische interventies. Hiermee kunnen mogelijk klachten worden gereduceerd. Ziektepercepties zijn ideeën die door de patient worden ontwikkeld om de ziekte te begrijpen en om zelf de controle te krijgen over de ziekte. Coping mechanismen zijn cognitieve en gedragsmatige

handelingen om met de ziekte om te kunnen gaan. In **hoofdstuk 5** worden resultaten besproken van een dwarsdoorsnede studie waarin aan de hand van het Common Sense Model (CSM), ontwikkeld door Leventhal et al., de relaties tussen ziektepercepties, coping mechanismen en ziekte uitkomsten bij IBD-patiënten worden beschreven. Leventhal et al. beschrijft aan de hand van het CSM dat ziektepercepties direct effect hebben op ziekte uitkomsten (kwaliteit van leven, werk productiviteit en activiteitenbeperking) maar ook indirect invloed hebben op deze ziekte uitkomsten via coping mechanismen. Resultaten gepresenteerd in dit hoofdstuk tonen aan dat patiënten die meer consequenties toeschreven aan de ziekte, meer persoonlijke controle en minder begrip voor hun aandoening hadden, het coping mechanisme 'verminderde fysieke activiteit' frequenter toepasten dan patiënten waarbij deze ziektepercepties niet aanwezig waren. En verminderde fysieke activiteit op zijn beurt was geassocieerd met een verminderde mentale en fysieke kwaliteit van leven en tevens meer activiteitenbeperking. Verminderde fysieke activiteit was in deze dwarsdoorsnede studie het enige coping mechanisme dat bijdroeg aan een indirect effect van ziektepercepties op uitkomsten. Hiernaast hadden ziektepercepties ook directe effecten op ziekte uitkomsten. Patiënten met weinig begrip voor het hebben van IBD en patiënten die negatieve emoties toeschreven aan het hebben van de ziekte, hadden een mindere mentale gezondheid. Tevens werd een lagere fysieke kwaliteit van leven en meer activiteitenbeperking gezien bij IBD-patiënten die ernstigere consequenties associeerden met hun aandoening. Het hebben van arthropathieën werd geassocieerd met een verminderde fysieke gezondheid, en meer werk- en activiteitenbeperking. In **hoofdstuk 7** wordt een longitudinale studie gepresenteerd waarbij IBD-patiënten gedurende 12 maanden zijn gevolgd. Na 12 maanden werden bij deze patiënten een verminderde kwaliteit van leven en werkproductiviteit gemeten. Factoren die zorgden voor een lagere kwaliteit van leven waren het hebben van arthropathieën, sterkere negatieve gedachten over de consequenties van IBD, meer negatieve gedachten over de emotionele impact op het dagelijks leven en meer activiteitbeperkingen. Verminderde werkproductiviteit was geassocieerd met arthropathieën en tevens negatieve ideeën over de ernst van de ziekte en de impact op het dagelijks functioneren.

Aangezien arthropathieën de meest voorkomende EIM bij IBD zijn, presenteren we in **hoofdstuk 6** de verschillen in ziektepercepties, coping mechanismen en uitkomsten tussen IBD-patiënten met en zonder arthropathieën. Wanneer dit verschil gemaakt zou kunnen worden, kan er een behandeling worden gestart

die meer afgestemd is op de klachten van de IBD patiënt met arthropathieën. Er wordt in dit hoofdstuk een mindere fysieke en mentale gezondheid en tevens meer activiteitbeperking bij IBD-patiënten met arthropathieën beschreven in vergelijking met patiënten zonder arthropathieën. Hiernaast waren patiënten met gewrichtsklachten zich meer bewust van hun symptomen en werd er meer variabiliteit en afwisseling in de symptomen ervaren. Tevens waren gewrichtsklachten bij IBD geassocieerd met negatieve consequenties, meer emotionele impact op het dagelijks leven en minder begrip voor de symptomen gerelateerd aan IBD en/of gewrichtsklachten vergeleken met de patiënten zonder arthropathieën. Patiënten met arthropathieën waren beter in staat om de aandacht af te leiden en aan leuke dingen te denken en waren meer sociaal naar anderen in vergelijking met patiënten zonder arthropathieën. Tevens werd in deze longitudinale studie de verandering van ziektepercepties, coping mechanismen en uitkomsten gedurende de 12 maanden follow-up besproken. Na 1 jaar waren patiënten met arthropathieën minder overtuigd van het effect van de (medicamenteuze) behandeling, maar waren ze desondanks beter in het aanpassen van hun dagelijkse activiteiten aan de ziekte vergeleken met het moment van inclusie.

De relatie tussen IBD en afwijkingen in de hersenen

Naast gewrichtsklachten, komen er ook nog verschillende andere EIMs voor bij IBD-patiënten. In de literatuur wordt een associatie beschreven tussen systemische inflammatie en veranderingen in de hersenen bij onder andere reumatoide artritis (RA)-patiënten. In **hoofdstuk 8** wordt het effect van systemische inflammatie en vermoeidheid beschreven aan de hand van verschillende MRI technieken en neuropsychologische onderzoeken bij CD-patiënten in remissie met vermoeidheidsklachten vergeleken met gezonde controles zonder vermoeidheidsklachten. Neurochemische, perfusie en mentale veranderingen werden aangetoond bij CD patiënten in vergelijking met gezonde controles. Een verminderde glutamine- en glutamaat-concentratie werd gevonden bij patiënten met CD. Glutamaat receptoren zijn aanwezig in de hypocampus en deze neurotransmitter is onder andere betrokken bij het geheugen en stemming. Glutamine zorgt voor het energie metabolisme in de hersenen. Naast een verschil in neurotransmitters tussen CD-patiënten en gezonde controles, werd een verhoogde cerebrale perfusie gezien bij CD-patiënten, waarschijnlijk als reactie op inflammatie. Depressieve symptomen en een lagere cognitieve score voor uitvoerende functies en geheugen waren meer frequent aanwezig bij CD-patiënten in vergelijking met gezonde controles.

ALGEMENE CONCLUSIE

Het herkennen van arthropathieën bij IBD en vooral het onderscheid maken tussen artralgie of SpA is voor veel MDL-artsen een uitdaging. Dit proefschrift geeft een aanbeveling hoe MDL-artsen gewrichtsklachten bij IBD kunnen herkennen en aan de hand van welke kenmerken er een onderscheid gemaakt kan worden tussen artralgie en SpA. Tevens wordt de impact van gewrichtsklachten op de kwaliteit van leven, ziekte percepties en coping mechanismen beschreven. Door meer inzicht in de etiologie van arthropathieën bij IBD te krijgen, kan mogelijk een behandeling op maat voor deze patiënten worden gemaakt. Patiënten met IBD en SpA dienen naar de reumatoloog te worden verwezen.

CHAPTER 11

Supplementary material
List of publications
List of abbreviations
Curriculum Vitae
Dankwoord

SUPPLEMENTARY MATERIAL

CHAPTER 3. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study.

Amor criteria for spondyloarthritis

Criteria	Points
Clinical symptoms or past history:	
Lumbar or dorsal pain during the night, or morning stiffness of lumbar or dorsal spine	1
Asymmetric oligoarthritis	2
Buttock pain	1
if affecting alternately the right or the left buttock	2
Sausage like digit or toe (dactylitis)	2
Enthesitis	2
Iritis	2
Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis	1
Acute diarrhoea accompanying, or within 1 month, the onset of arthritis	1
Presence or history of psoriasis, balanitis, or inflammatory bowel disease	2
Radiological finding:	
Sacroiliitis (grade > 2 if bilateral; grade > 3 if unilateral)	3
Genetic background:	
Presence of HLA-B27, or familial history of ankylosing spondylitis, Reiter syndrome, uveitis, psoriasis, or chronic enterocolopathies	2
Response to treatment:	
Good response to NSAIDs in less than 48 h, or relapse of the pain in less than 48 h if NSAIDs discontinued	2
HLA, human leukocyte antigen; NSAIDS, non-steroidal anti-inflammatory drugs. A patients is considered to have spondyloarthritis if the sum of the point counts is 6 or more. A total point count of 5 or more classifies for probable spondyloarthritis.	

European Spondyloarthropathy Study Group criteria for Spondyloarthritis

Inflammatory back pain	or	Synovitis - Asymmetric - Predominantly in the lower limbs

One or more of the following variables:
- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Urethritis, cervicitis, or acute diarrhea within one month before arthritis
- Buttock pain alternating between right and left gluteal areas
- Enthesitis (heel)
- Sacroiliitis

ASAS classification criteria for axial spondylarthritis

Sacroiliitis on imaging* plus ≥ 1 SpA feature#	or	HLA-B27 plus ≥ 2 other SpA features#

*Sacroiliitis on imaging
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Definite radiographic sacroiliitis according to mNY criteria

#SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- IBD
- Good response to NSAIDs
- Family history for SpA
- Elevated CRP

ASAS, The Assessment of SpondyloArthritis international Society; HLA, human leukocyte antigen; NSAIDS, non-steroidal anti-inflammatory drugs; SpA, Spondyloarthritis

ASAS classification criteria for peripheral spondyloarthritis

Arthritis* or enthesitis or dactylitis
plus

≥ 1 SpA feature
- Uveitis
- Psoriasis
- IBD
- Preceding infection
- HLA-B27
- Sacroiliitis on imaging

or

≥ 2 SpA features
- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain
- Family history for SpA

*Peripheral arthritis: usually predominantly lower limb and/or asymmetric arthritis. ASAS, The Assessment of SpondyloArthritis international Society; HLA, human leukocyte antigen; NSAIDS, non-steroidal anti-inflammatory drugs; SpA, Spondyloarthritis

Modified New York criteria for Ankylosing Spondylitis

Clinical criteria:
- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
- Limitation of motion of the lumbar spine in the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological criterion:
- Sacroiliitis grade > 2 bilaterally or grade 3-4 unilaterally.

Definite ankylosing spondylitis if the radiological criterion is associated with at least one clinical criterion

CHAPTER 7. 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.

Supplementary Material A. Demographic and clinical characteristics of completers (n=204) and non-completers (n=41).

Variable	Completers (n=204)	Non-completers (n=41)	P-value
Type of IBD, n (%)			
Crohn's disease	146 (71.6)	33 (80.5)	0.334
Ulcerative colitis	58 (28.4)	8 (19.5)	0.334
Age (years), mean (SD)	44.3 (13.7)	38.4 (11.4)	0.011
Male gender, n (%)	82 (40.2)	12 (29.3)	0.220
Current smoker, n (%)	47 (23.0)	10 (24.4)	0.497
Disease duration (years), median (SD)	15.0 (7.0-24.0)	13.0 (8.0-24.0)	0.641
Montreal classification			
Location CD, n (%)			
L1 ileal	36 (24.7)	10 (30.3)	0.513
L2 colonic	22 (22.6)	5 (15.2)	0.480
L3 ileocolonic	65 (44.5)	16 (48.5)	0.702
L1-3 + L4 upper	12 (8.2)	2 (6.1)	1.000
Behavior CD, n (%)			
B1 non-stricturing/penetrating	62 (42.5)	14 (42.4)	1.000
B2 stricturing	22 (15.1)	3 (9.1)	0.578
B3 penetrating	21 (14.1)	4 (12.1)	1.000
+ perianal disease	41 (28.1)	12 (36.4)	0.399
Extension UC, n (%)			
E1 ulcerative proctitis	4 (6.9)	2 (25.0)	0.151
E2 left sided UC	20 (34.5)	2 (25.0)	0.709
E3 extensive UC (pancolitis)	34 (58.6)	4 (50.0)	0.714
Current medication use, n (%)			
5-ASA	44 (21.6)	5 (12.2)	0.204
Steroids	10 (4.9)	3 (7.3)	0.461
Immunomodulators	45 (22.1)	8 (19.5)	0.837
Anti-TNF agents	56 (27.5)	14 (34.1)	0.449
Axial and/or peripheral joint complaints, n (%)	113 (55.4)	22 (53.7)	1.000
Peripheral joint complaints only	41 (36.3)	12 (54.5)	0.171
Back pain only	8 (7.1)	0 (0.0)	0.352
Mixed complaints	64 (65.6)	10 (45.5)	0.467

Supplementary Material B. Univariate analysis.

Variable	Outcome						Outcome			
	SIBDQ		SF-36 PCS		SF-36 MCS		Work impairment		Activity impairment	
	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value
Demographic and clinical characteristics										
Female gender	-5.579	0.000[a]	-4.008	0.000[a]	-2.235	0.026[a]	0.073	0.854	1.084	0.000[a]
Current smoker	-1.790	0.116	-1.213	0.230	-0.414	0.687	0.236	0.563	0.070	0.819
Active disease	-1.512	0.000[a]	-1.114	0.000[a]	-0.727	0.000[a]	0.437	0.000[a]	0.324	0.000[a]
Joint pain	-1.820	0.000[a]	-2.099	0.000[a]	-0.849	0.000[a]	0.394	0.000[a]	0.601	0.000[a]
Illness perceptions										
Identitiy	-1.531	0.000[a]	-1.472	0.000[a]	0.421	0.001[a]	0.321	0.000a	0.425	0.000[a]
Timeline chronic	-0.253	0.094	-0.241	0.072	-0.212	0.120	-0.138	0.009	0.049	0.227
Consequences	-1.134	0.000[a]	-1.015	0.000[a]	-0.808	0.000[a]	0.271	0.000[a]	0.289	0.000[a]
Personal control	0.369	0.006[a]	0.542	0.000[a]	0.421	0.001[a]	-0.032	0.506	-0.136	0.000[a]
Illness coherence	0.703	0.000[a]	0.292	0.015	0.880	0.000[a]	-0.173	0.000[a]	-0.115	0.001[a]
Timeline cyclical	-1.255	0.000[a]	-0.991	0.000[a]	-0.656	0.000[a]	0.241	0.000[a]	0.269	0.000[a]
Emotional representations	-1.008	0.000[a]	-0.502	0.000[a]	-1.039	0.000[a]	0.200	0.000[a]	0.199	0.000[a]
Coping										
Comforting cognitions	-0.027	0.808	-0.121	0.218	0.162	0.105	-0.022	0.568	-0.021	0.484
Decreasing activity	-0.870	0.000[a]	-0.870	0.000[a]	-0.774	0.000[a]	0.203	0.000[a]	0.266	0.000[a]
Diverting attention	-0.250	0.042	-0.275	0.012	-0.037	0.743	-0.008	0.859	0.032	0.334
Optimism	0.453	0.011	0.091	0.564	0.626	0.000[a]	-0.073	0.248	-0.098	0.041
Pacing	-0.470	0.000[a]	-0.676	0.000[a]	-0.332	0.000[a]	0.145	0.000[a]	0.175	0.000[a]
Creative solutions	-0.310	0.011	-0.418	0.000[a]	-0.112	0.313	0.073	0.118	0.070	0.032
Accepting	0.229	0.114	-0.110	0.392	0.128	0.329	-0.003	0.954	0.003	0.947
Consideration	-0.343	0.019	-0.348	0.007	-0.080	0.547	0.101	0.053	0.015	0.695

[a]Variables were entered into the linear mixed model.

LIST OF PUBLICATIONS

1. Van der Have M, Brakenhoff LK, **van Erp SJ**, Kaptein AA, Leenders M, Scharloo M, Veenendaal RA, van der Heijde DM, van der Meulen-de Jong AE, Hommes DW, Fidder HH. 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(3):276-83.

2. **Van Erp SJ**, Brakenhoff LK, van Gaalen FA, van den Berg R, Fidder HH, Verspaget HW, Huizinga TW, Veenendaal RA, Wolterbeek R, van der Heijde D, van der Meulen-de Jong AE, Hommes DW. Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow-up study. J Crohns Colitis 2016;10(2):166-75.

3. Severs M, **van Erp SJ**, van der Valk ME, Mangen MJ, Fidder HH, van der Have M, van Bodegraven AA, de Jong DJ, van der Woude CJ, Romberg-Camps MJ, Clemens CH, Jansen JM, van de Meeberg PC, Mahmmod N, Ponsioen CY, Bolwerk C, Vermeijden JR, Pierik MJ, Siersema PD, Leenders M, van der Meulen-de Jong AE, Dijkstra G, Oldenburg B; Dutch Initiative on Crohn and Colitis. Smoking is associated with extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10(4):455-61.

4. Verheul MK, **van Erp SJ**, van der Woude D, Levarht EW, Mallat MJ, Verspaget HW, Stolk J, Toes RE, van der Meulen-de Jong AE, Hiemstra PS, van Kooten C, Trouw LA. Anti-carbamylated protein antibodies: a specific hallmark for rheumatoid arthritis. Comparison to conditions known for enhanced carbamylation; renal failure, smoking and chronic inflammation. Ann Rheum Dis 2016;75(8):1575-76.

5. **Van Erp SJ**, Leicher LW, Hennink SD, Ghorbanoghli Z, Breg SA, Morreau H, Nielsen M, Hardwick JC, Roukema JA, Langers AM, Cappel WH, Vasen HF. Identification of familial colorectal cancer and hereditary colorectal cancer syndromes through the Dutch population-screening program: results of a pilot study. Scand J Gastroenterol 2016;51(10):1227-32.

6. **Van Erp SJ**, Brakenhoff LK, Vollmann M, van der Heijde D, Veenendaal RA, Fidder HH, Hommes DW, Kaptein AA, van der Meulen-de Jong AE, Scharloo M. Illness perceptions and outcomes in patients with inflammatory bowel disease: is coping a mediator? Int J Behav Med 2017;24(2):205-14.

7. **Van Erp SJ**, Verheul MK, Levarht EW, van der Reijden JJ, van der Heijde D, van Gaalen FA, Hommes DW, Norman GL, Shums Z, Mahler M, Verspaget HW, Trouw LA, van der Meulen-de Jong AE. Short article: Absence of serological rheumatoid arthritis biomarkers in inflammatory bowel disease patients with arthropathies. Eur J Gastroenterol Hepatol 2017;29(3):345-48.

8. **Van Erp S,** Ercan E, Breedveld P, Brakenhoff L, Ghariq E, Schmid S, van Osch M, van Buchem M, Emmer B, van der Grond J, Wolterbeek R, Hommes D, Fidder H, van der Wee N, Huizinga T, van der Heijde D, Middelkoop H, Ronen I, van der Meulen-de Jong A. Cerebral magnetic resonance imaging in quiescent Crohn's disease patients with fatigue. World J Gastroenterol 2017;23(6):1018-29.

9. **Van Erp SJ,** van der Have M, Fidder HH, van der Heijde D, Wolterbeek R, Hommes DW, Kaptein AA, van der Meulen-de Jong AE. The impact of arthropathies on illness perceptions, coping strategies, outcomes and their changes over time in IBD patients: a 12-month follow-up study. Eur J Gastroenterol Hepatol 2018

LIST OF ABBREVIATIONS

ADM	Adrenomedullin
ASL	Arterial spin labeling
AQP	Aquaporin
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-CarP	Anti-Carbamylated protein
Anti-CCP	Anti-Cyclic citrullinated peptide
Anti-CBir1	Anti-flagellin
Anti-OmpC	Anti-Eschericia coli outer membrane porin c
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASCA	Anti-Saccharomyces cerevesiae
axSpA	Axial spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
CARD	Caspase recruitment domain-containing protein
CBF	Cerebral blood flow
CBP	Chronic back pain
CBT	Cognitive behavioral therapy
CD	Crohn's disease
CFS	Chronic fatigue syndrome
Cho	Choline
CORS	Coping with rheumatic stressors questionnaire
Cr	Creatine
CRP	C-reactive protein
CSF	Cerebral spinal fluid
CSM	Common sense model
CT	Computerized tomographic
CXCL	Chemokine ligand
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DTI	Diffusion tensor imaging
E. Coli	Escherichia coli
EIM	Extra-intestinal manifestation
ELISA	Enzyme-linked immunosorbent assay
ERAP	Endoplasmic reticulum aminopeptidase

ESSG	European Spondyloarthropathy Study Group
FA	Fractional anisotropy
fCAL	Feces calprotectein
Gln	Glutamine
Glu	Glutamate
GM	Grey matter
HADS	Hospital anxiety depression scale
HBI	Harvey-Bradshaw index
HC	Heavy chain
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IC	Indeterminate colitis
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin
Ins	myo-inositol
IMID	Immune-mediated inflammatory disease
IPQ-R	Revised illness perception questionnaire
IQR	Interquartile range
IU	Institutional units
JAK	Janus kinase
LOF	Loss-of-function
LUMC	Leiden university medical center
MASES	Maastricht ankylosing spondylitis enthesitis score
MCP	Monocyte chemoattractant protein
MCS	Mental component score
MD	Mean diffusivity
MDD	Major depression disorder
MFI	Multidimensional fatigue index
MHC HC	Major histocompatibility heavy chain complex
MICA	MHC class I chain-like gene a
MiRNA	MicroRNA
MMSE	Minimal mental state examination
mNY	modified New York
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis

MTI	Magnetization transfer imaging
MTR	Magnetization transfer ratio
NAA	N-acetyl-aspartate
NAAG	N-acetyl-aspartyl-glutamate
NAMPT	Nicotinamide phosphoribosyltransferase
NK	Natural killer
NOD	Nucleotide-binding oligomerization domain-containing protein
NRS	Numeric rating scale
OA	Osteoarthritis
OCTN	Organic cation/carnitine transporter
OWD	Occiput-to-wall distance
PCA	Principal components analysis
PCR	Polymerase chain reaction
PCS	Physical component score
pJTC	Peripheral joint complaints
PLD	Post labelling delay
PsA	Psoriatic arthritis
PSC	Primary sclerosing cholangitis
pSpA	Peripheral spondyloarthritis
pSS	primary Sjogren syndrome
QoL	Quality of life
RA	Rheumatoid arthritis
SCCAI	Simple clinical colitis activity index
SCWT	Stroop-color-word test
SD	Standard deviation
SF	Short form
SI	Sacroiliitis
SIBDQ	Short inflammatory bowel disease questionnaire
SpA	SpondyloArthritis
STAT	Signal transducer and activator of transcription
TNF	Tumor necrosis factor
TMT	Trail making test
TYK	Tyrosine kinase
UC	Ulcerative colitis
UPR	Unfolded protein response
uSpA	Undifferentiated SpA
VAS	Visual analogue scale
VBM	Voxel based morphometry

WAIS-R	Revised wechsler adult intelligence scale
WFT	Word fluency test
WM	White matter
WMS-R	Revised wechsler memory scale
WPAI	Work productivity and activity impairment questionnaire

CURRICULUM VITAE

Sanne van Erp was born on May 17th 1991, in Made, the Netherlands. In 2010, she finished the Gymnasium at the Mencia de Mendoza Lyceum in Breda and moved to Leiden to study Medicine at the Leiden University. During college, the interest in the field of Gastroenterology and Hepatology developed. In 2012, she contributed to a research project at the department of Gastroenterology and Hepatology of the Leiden University Medical Center (LUMC) under supervision of dr. A.E. van der Meulen-de Jong. In 2014 she started with her medical research internship for four months at the Stichting Opsporing Erfelijke Tumoren (STOET) about the identification of familial colorectal cancer in the Dutch population screening program under supervision of Prof. dr. H.F. Vasen. After this, she continued research in the field of Gastroenterology from November 2014 as a PhD-student at the department of Gastroenterology and Hepatology of the LUMC on arthropathies in IBD under supervision of Prof. dr. D.W. Hommes, Prof. dr. D. van der Heijde and dr. A.E. van der Meulen-de Jong. She performed research for one year full-time before starting her internships. In January 2016, she started with the medical internships and combined this with finishing her PhD traineeship. Results are presented in this thesis. In May 2018, Sanne will start with her residency in Internal Medicine, as the first part of her residency program of Gastroenterology and Hepatology.

DANKWOORD

Dit proefschrift zou niet tot stand zijn gekomen zonder de steun van velen. Een aantal zou ik graag in het bijzonder willen noemen.

Als eerste wil ik graag mijn co-promotor dr. A.E. van der Meulen-de Jong en promotoren Prof. dr. D.W. Hommes en Prof. dr. D. van der Heijde bedanken. Beste Andrea, dank voor jouw inzet en intensieve begeleiding de afgelopen jaren; zonder jouw hulp en vertrouwen zou ik hier vandaag niet staan. Hiernaast wil ik je bedanken voor de mogelijkheden die je voor me hebt gecreëerd binnen de afdeling Maag-, Darm-, en Leverziekten.

Beste Daan, dank voor onze prettige samenwerking ondanks het tijdsverschil en een aantal kilometers afstand. Dankzij jouw enthousiasme en creativiteit heeft dit proefschrift vorm gekregen.

Beste Désirée, door jou heb ik inhoudelijk veel geleerd over de verschillende soorten gewrichtsklachten en de classificatie hiervan. Jouw passie voor onderzoek in combinatie met jouw kritische blik heeft ervoor gezorgd dat hier nu een mooi proefschrift ligt; ik wil je hier graag voor bedanken.

Tevens wil ik graag alle co-auteurs bedanken voor de prettige samenwerking. Beste Mike van der Have, Margeet Scharloo, Manja Vollmann en Ad Kaptein, dank voor jullie hulp en grondige feedback op de kwaliteit van leven manuscripten. Beste Floris van Gaalen, dank dat je mij de basis van de reumatologie hebt geleerd. Beste Leendert Trouw, dank voor de mogelijkheid dat je mij naast klinisch onderzoek kennis hebt laten maken met onderzoek op het lab. Nivine Levarht en Johan van der Reijden, dank voor de hulp hierbij. Beste Ece Ercan, Itamar Ronen en Huub Middelkoop, veel dank voor de waardevolle samenwerking met betrekking tot de pilot-studie beschreven in hoofdstuk 8.

Collega's van de Maag-, Darm-, Leverziekten uit het LUMC. Dank voor de mogelijkheid om promotieonderzoek op jullie afdeling te doen. Ik heb het tot op de dag van vandaag als een prettige omgeving ervaren. Hans Vasen en Simone Hennink, van jullie heb ik de beginselen van het onderzoek geleerd. Hier heb ik enorm veel baat bij gehad als voorbereiding op mijn promotie onderzoek, dank hiervoor. Beste Niene Peek, wat leuk dat wij samen, mede door een goede samenwerking, 'Grip op Pijn' hebben opgezet.

Collega's en vrienden van het lab; wat heb ik een ongelofelijk leuk fulltime promotiejaar met jullie gehad. Eveline, Marij, Johan en Wim, dank voor jullie hulp en gezelligheid. Annarein, Danny, Claire, Ilse, Marieke, Lennart, Mark, Madelon en Luuk wat hebben we zowel binnen als buiten het LUMC veel leuke dingen met elkaar gedaan. Ik kijk terug op een onvergetelijke tijd.

Mijn paranimfen, Annarein en Inge. Lieve Rein, wat hebben wij elkaar de afgelopen jaren goed leren kennen. Je bent een vriendin die altijd voor me klaarstaat en wat bewonder ik jouw gedrevenheid en discipline. Lieve Inge, lieve Kit. Enorm bijzonder dat je vandaag naast me staat als paranimf. Wat ben ik als oudere zus trots op wat je allemaal doet naast de studie geneeskunde!

Lieve neusjes; Bob, Sam en Dex, lieve jaarclubgenoten, lieve (oud)huisgenoten uit Leiden en lieve co-groepgenoten, dank voor jullie steun, gezelligheid en afleiding.

Stef en Inge, wat hebben wij een bijzondere band met zijn drieën. Ik ben trots op jullie!

Lieve papa en mama, jullie hebben me altijd gestimuleerd te doen wat ik ambieer. Ik heb enorm veel van jullie geleerd en ik weet dat ik altijd op jullie kan terugvallen. Papa, jouw adviezen zijn altijd heel waardevol. In het doen en laten lijken wij op elkaar en je hebt daarom aan een half woord genoeg. Mama, jij hebt me geleerd rust te nemen en te relativeren. Jullie zijn van onschatbare waarde.

Tot slot, lieve Wout, jij bent mijn grote steun en toeverlaat. Het afgelopen anderhalf jaar heb ik mijn promotieonderzoek met name in mijn vrije tijd gedaan. Desalniettemin was je er altijd voor mij. Dank voor jouw liefde, motivatie en geduld.