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

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CHAPTER 2

Common pathophysiology between inflammatory bowel disease and spondyloarthritis: a review

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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, microbiological, 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, microbiological, 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-1 β 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-1 β , 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 sacroiliitis 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-1 β 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 pre-disposing. 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 (*STAT3*). Other noteworthy susceptibility genes in IBD are the nucleotide-binding oligomerization domain-containing gene (*NOD2*), the caspase recruitment domain-containing gene (*CARD9*) and the autophagy-related gene (*ATG16L1*).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 (*ERAP1*) 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 (*PSMG1/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 system 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-B27* 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 (*MAP1LC3A*) 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 complaints 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

CHAPTER 2

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 cerevisiae (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-Escherichia 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 calprotectin (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 be 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, microbiological 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 (1 α ,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃)) 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.

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