The joint–gut axis in inflammatory bowel diseases

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Abstract
Inflammatory bowel diseases, Crohn’s disease and ulcerative colitis, are associated with a variety of extraintestinal manifestations. The most common extraintestinal manifestation, articular involvement, occurs in 16% to 33% of inflammatory bowel disease patients. These arthropathies may increase morbidity, resulting in a worse quality of life compared with inflammatory bowel disease patients without arthropathies. Thus, arthropathies in inflammatory bowel diseases represent a major medical problem in these patients. Arthritis associated with inflammatory bowel diseases is one of the diseases captured under the umbrella of spondyloarthritis. Spondyloarthritis is a group of inflammatory diseases with overlapping features and is linked to Human Leukocyte Antigen-B27. Arthropathy in inflammatory bowel diseases is clinically divided into peripheral and axial involvement. Peripheral arthritis often flares with relapses of bowel disease resulting in a different treatment approach than axial arthritis in which the course is independent of inflammatory bowel disease activity. Definitions, prevalence, pathophysiology and treatment of the arthropathies commonly seen in inflammatory bowel diseases such as peripheral arthritis, dactylitis, enthesitis, arthralgia, sacroiliitis, inflammatory back pain and ankyllosing spondylitis are summarized.

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Abbreviations: SpA, spondyloarthritis; AS, ankylosing spondylitis; IBP, inflammatory back pain; SI, sacroiliac; ASAS, The Assessment of SpondyloArthritis international Society.
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1. Introduction

Inflammatory bowel diseases (IBD), with its major forms Crohn’s disease (CD) and ulcerative colitis (UC), are chronic diseases with a relapsing and remitting clinical course arising from an interaction between genetic and environmental factors. The precise etiology is still unknown and therefore a causal treatment is not yet available.

Apart from intestinal symptoms, IBD is associated with a variety of extraintestinal manifestations (EIMs), with a reported prevalence varying from 6 to 36%. These EIMs are occasionally the presenting symptom. The most common EIM in CD and UC is articular involvement but, cutaneous, ocular, hepatobiliary and hematologic manifestations may also occur.

The prevalence rates of arthropathy in IBD range between 16% to 33% in both retrospective and prospective studies. Arthropathy in IBD patients is clinically divided into peripheral and axial involvement. Peripheral arthritis (asymmetrical, predominantly in the lower extremities) and/or inflammatory spinal pain in IBD patients, with consistent absence of the rheumatoid factor, is classified as one of the spondyloarthritis (SpA) according to the most well-known classification criteria the European Spondyloarthropathy Study Group (ESSG). SpA is a group of inflammatory diseases with overlapping features (e.g. psoriasis, uveitis and IBD) and is linked to Human Leukocyte Antigen (HLA)-B27. Other diseases included in the SpA group are ankylosing spondylitis (AS), undifferentiated SpA, arthritis associated with acute anterior uveitis, psoriatic arthritis, reactive arthritis and idiopathic arthritis.

The definitions for peripheral and axial arthropathies commonly used will be summarized. The peripheral arthropathies in IBD that will be discussed here includes peripheral arthritis, enthesitis, dactylitis and arthralgia, and the axial arthropathies associated with IBD includes isolated sacroiliitis, inflammatory back pain (IBP) and AS (Table 1).

2. Definitions and clinical manifestations

2.1. Peripheral arthropathies

2.1.1. Peripheral arthritis

In 1998, the Oxford research group suggested that peripheral arthritis (without axial involvement) could be divided into two groups: an oligoarticular large joint arthritis and a bilateral symmetrical polyarthritis based on the different distribution and natural history. Ever since, this division is commonly used in gastroenterology research studies on arthropathy in IBD patients, but remained rather unknown in rheumatology literature. Orchard et al. defined type 1 (pauci/oligoarticular) peripheral arthritis as joint pain with the evidence of swelling or effusion affecting fewer than 5 joints and mainly affecting the large weight bearing joints of the lower limbs. These joint symptoms are usually acute and self-limiting, resolve in less than 10 weeks, leave no permanent joint damage and mostly occur during exacerbations of IBD activity. Type 2 (polyarticular) peripheral arthritis affects more than five joints, with a symmetrical distribution and affects predominantly the small joints of the
Peripheral arthritis in IBD patients is mostly asymmetric and upper limbs. Symptoms persist in episodes for months to years and follow a course independent of the activity of IBD.

Studies using the gut axis in inflammatory bowel diseases vary widely from 2 to 32%. Variations in prevalence in IBD patients ranges from 7 to 16%, and one smaller study showed a prevalence of 30%. Studies on arthropathy in IBD patients. Two large studies reported a prevalence of 2% and 4% of dactylitis in IBD patients. Arthralgia, thus representing a major medical problem in IBD patients.

**2.1.2. Enthesitis and dactylitis**

Enthesitis and dactylitis in IBD patients have been studied less well than peripheral arthritis. Peripheral enthesitis is an inflammation of the site where a tendon inserts the bone, for example, the insertion of the Achilles tendon into the calcaneus. Patients may suffer from severe pain, tenderness and swelling. In small studies, the prevalence of enthesitis in IBD ranges from 5–10%, 5,9,11,16

Peripheral dactylitis, also known as sausage-like toe or sausage-like finger, is a characteristic and highly specific feature of SpA. Clinical examination shows a painful and diffuse swelling of the entire digit due to flexor tenosynovitis and marked adjacent soft tissue swelling in which small joint synovitis may occur. Salvarani et al.9 and Palm et al.16 respectively reported a prevalence of 2% and 4% of dactylitis in IBD patients.

**2.1.3. Arthralgia**

Arthralgia is (non-inflammatory) joint pain without objective evidence of swelling or effusion and has been excluded in most studies on arthropathy in IBD patients. Two large studies reported a prevalence of arthralgia in IBD patients of 8% and 16% and one smaller study showed a prevalence of 30%. Palm et al.19 investigated the impact of non-inflammatory joint pain in IBD patients on health related quality of life (HRQOL assessed by SF-36 and IBDQ). They found arthralgia in 85 (16%) of the 521 patients and these patients had a significantly lower HRQOL score indicating a worse health related quality of life compared with IBD patients without arthralgia, thus representing a major medical problem in IBD patients.

**2.2. Axial arthropathies**

Axial arthropathy associated with IBD includes isolated sacroiliitis, IBD and AS. The onset of axial involvement frequently precedes that of IBD, the course is independent of the IBD course and bowel surgery does not alter the course of associated sacroiliitis or AS.

**2.2.1. Isolated sacroiliitis**

Isolated sacroiliitis is an inflammation of the sacroiliac (SI) joints, consisting of uni- or bilaterally inflammation, which is mostly asymptomatic. Symptomatic patients may present with pain in the pelvis and/or decreased spinal mobility. Sacroiliitis is diagnosed by imaging methods such as conventional radiographs and CT showing sclerosis, erosions and/or ankylosis, or by MRI showing acute inflammation with or without structural changes. The prevalence of sacroiliitis in IBD patients in studies varies widely from 2 to 32%, 5,11,12,16,21,22 Dekker et al.12 found

| Table 1 Definitions and prevalence of the arthropathies in IBD. |
|-----------------|-----------------|-----------------|
|                 | Definitions     | Prevalence      |
| Peripheral arthropathies |                 |                 |
| Peripheral arthritis | Joint swelling and joint pain | 7–16% |
| Type 1 peripheral arthritis | < 5 joints | 4–8% |
| Type 2 peripheral arthritis | Mainly large weight bearing joints of the lower limbs | 1–3% |
| Type 1 peripheral arthritis | Acute, self-limiting attacks (<10 weeks) | 1–3% |
| Type 2 peripheral arthritis | Association with bowel activity* | 1–3% |
| Type 2 peripheral arthritis | 5 joints | 1–3% |
| Enthesitis | Pain and swelling at the site where a tendon inserts the bone | 5–10% |
| Dactylitis | “Sausage-like digit” | 2–4% |
| Arthralgia | Joint pain (without swelling) | 8–30% |

Axial arthropathies

Isolated sacroiliitis

Diagnosis based on imaging techniques showing sclerosis, erosions and/or ankylosis of the sacroiliac joint

Inflammatory back pain

The Calin criteria are fulfilled if at least four out of the five characteristics are present: Age of onset 40 years Insidious onset Duration 3 months Association with morning stiffness Improvement after exercise

Ankylosing spondylitis

Diagnosis based on a combination of inflammatory back pain symptoms, limitation in spinal mobility and imaging techniques showing bilateral sacroiliitis grade 2 or unilateral sacroiliitis grade 3–4

25 The joint...
no association between the radiographic grading of sacroiliitis and part of bowel involvement, or extent of bowel involvement in a group of 109 IBD patients with sacroiliitis. Furthermore, there was no correlation between the radiographic grading of sacroiliitis and the duration of bowel disease. In contrast, de Vlam et al.\textsuperscript{11} found sacroiliitis to be more prevalent in patients with disease duration over 10 years compared to those with a duration of 5 or less years.

\subsection{2.2.2. Inflammatory back pain}
IBP, a consequence of inflammation of the SI joints that may spread to the spine in the majority of patients, is the major clinical symptom of AS and several clinical classification criteria exist to differentiate between inflammatory and mechanical back pain\textsuperscript{10,23,24}. IBP is characterised by an insidious onset, improves after exercise but not with rest, and is associated with morning stiffness. It may also present as pain during the second half of the night and/or alternating buttock pain. The most frequently used set of criteria for IBP is the Calin criteria (Table 1).\textsuperscript{23} In studies that use these criteria the prevalence of IBP in IBD patients ranges from 5\%–30\%,\textsuperscript{5,8–11,16}

\subsection{2.2.3. Ankylosing spondylitis}
AS, the most typical representation of SpA, is a chronic inflammatory disease of the axial skeleton (spondylitis, spondylodiscitis, spondyloarthritis and/or sacroiliitis), in which other locations in the body can also be affected e.g. peripheral arthritis and enthesitis. AS most often affects white males with onset between 15 and 40 years of age and causes symptoms of inflammatory low back pain with peripheral arthritis and enthesitis. AS most often affects (that will be classified as AS) and also patients with chronic back pain who have not yet developed radiographic sacroiliitis (early stage of AS).\textsuperscript{29,30} In addition, patients without sacroiliitis on imaging can be classified as having axial SpA if they are HLA-B27 positive and have two additional clinical features. IBD is one of the possible clinical features. Patients presenting with arthritis, enthesitis and dactylitis in combination with 1–2 other clinical features (again IBD is one of these features) are classified as having peripheral SpA (unpublished data/to be published: Rudwaleit et al. New ASAS classification criteria for peripheral spondyloarthritis (abstract EULAR 2009) Ann Rheum Dis 2009;68(Suppl3):127).

In conclusion, arthropathy in IBD is divided into peripheral and axial involvement and may be classified as SpA. Most studies focus on peripheral arthritis, isolated sacroiliitis, IBP and AS in IBD patients. The type 1 and 2 subdivision in peripheral arthritis is rather unknown in rheumatology literature and therefore, possibly of limited value for clinical diagnosis of peripheral arthritis in IBD patients.

\section{3. Laboratory}
There is no reliable laboratory test that can be used as a diagnostic tool in the management or diagnosis of arthropathy in IBD.

\subsection{3.1. HLA-B27}
A strong association exists between HLA-B27 and AS patients in whom more than 90\% of patients are HLA-B27 positive. The frequency of HLA-B27 in IBD patients was found to be similar to the general population. On the other hand, 25–78\% of IBD patients with AS are HLA-B27 positive.\textsuperscript{16,31–33} In contrast, isolated sacroiliitis in CD patients is unrelated to HLA-B27.\textsuperscript{22,31,33}

\subsection{3.2. Anti-CCP}
Antibodies recognizing cyclic citrullinated peptides (anti-CCP) are highly specific for rheumatoid arthritis. Koutroubikas et al.\textsuperscript{34} investigated the prevalence of anti-CCP in a group of 222 IBD patients (history of arthritic involvement in 16.7\% IBD patients, 70 RA patients and 103 healthy controls). They found no differences in the prevalence of anti-CCP between IBD patients and healthy controls and between IBD

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
\textbf{Clinical criteria} \\
\hline
Low back pain and stiffness for more than 3 months, which improve with exercise, not relieved by rest. \\
Limitation of motion of the lumbar spine in both the sagittal and frontal planes. \\
Restriction of chest expansion relative to normal values corrected for age and sex. \\
Radiological criterion \\
Bilateral sacroiliitis grade \textgreater{}= 2 or unilateral sacroiliitis grade 3–4. \\
Definite ankylosing spondylitis if the radiological criterion is associated with at least one clinical criterion. \\
\hline
\end{tabular}
\caption{Modified New York criteria for ankylosing spondylitis.\textsuperscript{25}}
\end{table}
patients with or without arthritic manifestations, suggesting that the development of arthropathy in IBD patients is not correlated to the presence of anti-CCP.

Statements

- No reliable laboratory test for the management or diagnosis of arthropathies in IBD patients exists.
- AS but not sacroiliitis in IBD patients is associated with HLA-B27.
- Arthropathy associated with IBD is unrelated to anti-CCP.

4. Imaging

4.1. Peripheral arthropathies

Peripheral arthritis in IBD patients is usually nondeforming and nonerosive. Therefore, radiographs of peripheral joints do not show erosions. Mielants et al. found destructive lesions of the small joints, mainly metacarpophalangeal and metatarsal joints, more frequently in SpA patients presenting subclinical inflammatory gut lesions, predominantly of the chronic type, than in patients without gut inflammation.

Ultrasoundography and MRI studies on dactylitis showed fluid collection in the flexor synovial sheaths (flexor tenosynovitis) and soft tissue oedema with a variable degree of small joint synovitis.

4.2. Axial arthropathies

Diagnosis of sacroiliitis (often asymptomatic) is based on imaging techniques, in which plain radiography of the AP pelvis remains the most widely accepted and available initial screening method. Advanced inflammation results in sclerosis and cartilage destruction, eventually leading to syndesmophytes and partial/total ankylosis of the SI joints. There is a prolonged interval between the onset of inflammation of the SI joints and/or IBP symptoms and the appearance of objective radiographic findings of sacroiliitis. This prolonged interval is due to limitations of the diagnostic capacity of radiographs which is partly explained by the 2-dimensional imaging of the anatomically complex SI joints. Several studies reported a considerable intra- and interobserver variability in diagnosing radiographic sacroiliitis, with most variability occurring in stages 1 (suspicious changes) and 2 (minimal, abnormal changes with erosions or sclerosis). As a result, a delay of 5–10 years may occur in the diagnosis of AS according to the modified New York criteria in which radiographic sacroiliitis of at least grade 2 bilaterally or grade 3 unilaterally is needed (Table 2). The prevalence rate of radiographic sacroiliitis is probably underestimated as reflected by higher prevalence rates found in studies using more sensitive imaging techniques than plain radiographs. In 2008, Song et al. performed a systematic literature research to assess the diagnostic value of scintigraphy in detecting sacroiliitis in patients with SpA. They reported a sensitivity of a positive scintigraphy of the SI joints of 52% and a specificity of 78% and concluded that there are too many non-specific factors such as movement of the patient during the examination, age, and technical problems that may influence the accumulation of radiopharmaceuticals at normal bony sites to use a positive scintigraphy alone for the diagnosis of sacroiliitis. CT and MRI have the advantage of improved view of the complex anatomy of the SI joints in comparison to radiography and scintigraphy. CT reveals early bone changes such as erosions and sclerosis, but is unable to differentiate between active and inactive sacroiliitis. MRI may show abnormalities of bone, cartilage and soft tissues and detect active sacroiliitis, especially in the early phase of disease when no chronic changes are detectable and therefore, has been of much additional diagnostic benefit in early disease. In may 2009, a group of rheumatologists and radiologists (ASAS/OMERACT MRI working group) with experience in SpA and MRI described MRI findings of sacroiliitis and also proposed a definition for active sacroiliitis. They found that active inflammation of the SI joints in SpA patients detected by MRI includes bone marrow edema / osteitis, synovitis, enthesitis and capsulitis. The ASAS/OMERACT MRI working group defined active sacroiliitis on MRI (positive MRI) when bone marrow edema or osteitis is present.

Radiographic changes of chronic inflammatory and destructive spinal involvement in AS are sclerosis and syndesmophytes, but also vertebral bridging and fusion producing the classical “bamboo spine” may be seen. MRI visualizes both acute and chronic inflammation of the spine in SpA patients.

Thus, plain X-rays do not detect acute inflammation but rather chronic changes as a consequence of chronic inflammation of the SI joints as well as the spine. In contrast, MRI shows active sacroiliitis and inflammation of the spine and recently, a definition for active inflammation of the SI joints on MRI, a positive MRI, has been proposed.

Statements

- Imaging of the joints of IBD patients with peripheral joint symptoms are not required as a diagnostic tool and are usually nondeforming and nonerosive.
- Plain radiographs detect chronic but do not detect acute inflammation of the SI joints and the spine.
- A positive scintigraphy alone for diagnosing sacroiliitis should not be used due too many non-specific factors.
- MRI visualizes both acute and chronic inflammation of the SI joints and the spine resulting in early detection of sacroiliitis and AS.
- Imaging (radiographs and/or MRI) of the SI joints and spine is necessary in all IBD patients with high suspicion of sacroiliitis, IBP or AS.

5. Pathophysiology

The close relationship between joint and gut inflammation has been confirmed by several studies. The prevalence of articular involvement in IBD patients ranges from 16–33%. On the other hand, involvement of the gastrointestinal tract as
feature of SpA was found in about 70% of patients and in the long term, 7% to 12% of patients with SpA will develop overt IBD, suggesting a shared aetiology.52–55

5.1. Lymphocyte recirculation and homing to gut

Naive lymphocytes recirculate between the blood and lymphoid tissues in search of their cognate antigens that are transported to the immune system via the gut epithelium and translocate through specific epithelial cells of the intestine, the M cells, into underlying Peyer’s patches (secondary lymphoid tissue). The lymphocyte recirculation directs naive lymphocytes into the Peyer’s patches in a multistep extravasation cascade by recognizing the endothelial lining of high endothelial venules (HEVs, specialized postcapillary venules). When a lymphocyte finds its cognate antigen, processed by professional antigen-presenting cells, the cell becomes activated within the germinal centres (B cell) or outside the centres (T cell) in mesenteric lymph nodes, starts to proliferate and differentiate and return to the systemic circulation via the efferent lymphatic system. Following imprinting, the activated mucosal immunoblast goes back to the lamina propria of the gut, where it exerts its effector functions.56,57 In inflammation, changes occur in the mucosal vasculature, including vasodilatation, hyperaemia and increased permeability of the vessel wall, which are induced by the release and actions of various inflammatory mediators, resulting in enhanced extravasation of leukocytes.58–61 Furthermore, the migration pathways of lymphocytes are altered by aberrant expression patterns of adhesion molecules and chemokines, and these may provide an explanation for the pathogenesis of some extraintestinal manifestations in IBD.56,57

5.1.1. Do intestinal lymphocytes traffic to the joints?

In vitro binding assays revealed that activated human intestinal immunoblasts adhere efficiently both to intestinal mucosa and synovial HEVs, but do not bind to peripheral lymph node vasculature, suggesting that intestinal lymphocytes have the capacity to enter the joints.62 May et al.63 provided the first experimental support for the hypothesis that intestinal T cells activated by antigen migrate to the joints and induce synovial inflammation, known as the “gut iiteropathy concept”. They identified two CD8+ T cell clones with similar expression patterns of cytokines, which did not correspond to classical Th1/Th2 cytokine patterns (interferon-gamma, interleukin (IL)-4, tumour necrosis factor-α and IL-10 production). The T cell clones showed an identical tissue distribution, and were present in the intestinal mucosa, the synovium and the peripheral blood in a patient with enteropathic SpA.

Less is known about the endothelial adhesion molecules in synovial membrane that direct homing of activated, gut-derived leukocytes to joints. Naive lymphocytes leave the blood via a multistep cascade, consisting of rolling, activation, firm adhesion and transmigration using several adhesion molecules and chemotactic signals. Lymphocytes adhere to mucosal HEVs by using the mucosal homing receptor integrin α4β7 and its endothelial ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on HEVs in Peyer’s patches and flat-walled venules in lamina propria. MAdCAM-1 belongs to the immunoglobulin superfamily. Human mucosal lymphocytes do not use α4β7 to adhere to HEVs of inflamed synovium,62 and therefore, Salmi et al.64 determined which endothelial adhesion molecules in inflamed synovium support the binding of mucosa-derived leukocytes. They immunohistochemically stained synovectomy specimens from 20 patients with chronic arthritis and found that intercellular adhesion molecule-1 (ICAM-1/CD54) and vascular adhesion protein-1 (VAP-1) are most prominently expressed in synovial vessels, whereas inflamed synovial vasculature completely lacks MAdCAM-1. Furthermore, VAP-1 was a dominant endothelial ligand in supporting the adherence of small lymphocytes (naive cells and memory cells) and, in particular, large immunoblasts of gut. In contrast, mucosa-derived macrophages display a completely different pattern of recognition of vessels in inflamed synovium using endothelial P-selectin. So, only blocking the P-selectin interaction is not enough to block the inhibition of small lymphocytes and immunoblasts trafficking to inflamed synovial HEVs.64 In 2001, the same group65 determined that gut-derived mucosal leukocytes from IBD patients are capable of binding to vessels in inflamed synovium. They also found that small intestinal lymphocytes use multiple adhesion molecules and their corresponding endothelial ligands (CD18-ICAM-1, α4β7-VCAM-1, L-selectin-peripheral lymph node addressins, and CD44) to adhere to synovial vessels. Binding of activated immunoblasts and macrophages in IBD patients mostly relies on VAP-1 and P-selectin and its ligand P-selectin glycoprotein ligand-1 (PSGL-1) interactions. This is in concert with the results of their previous study published in 1997 in which they included normal gut. Furthermore, blocking of VAP-1 inhibited binding of all leukocytes to joint vessels.65

In conclusion, activated intestinal lymphocytes in IBD patients adhere to inflamed synovial vessels using multiple adhesion molecules and their counter receptors, of which VAP-1 supports the binding of all leukocytes. These findings provide an explanation for the pathogenesis of joint inflammation in IBD patients.

5.2. NOD2

The prevalence of mutations in the NOD2 gene (R702W, G908R, and 1007 fs) in CD patients is about 20–30% in the Western world.66 The risk of developing CD is 20–40 times higher in individuals that are homzygotic or compound heterozygotic for mutations in NOD2, whereas this risk is approximately four times higher in individuals that are heterozygous.66–69 The NOD2 gene plays a role in the innate immune response by activating nuclear factor-κB. Nuclear factor-κB is a key transcriptional regulator controlling the expression of a large number and variety of genes encoding proinflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes.70 Mutant NOD2 results in a disturbed cellular response to bacterial components like muropeptide N-acetylmuramic-L-Ala-L-Glu and lipo polysaccharides, leading to intracellular persistence of pathogens.71,72 So far, the exact mechanism in the link between NOD2 mutations and CD development is still unknown.

5.2.1. Are NOD2 carriers at risk for developing arthropathy?

Some studies have been carried out to search for an association between NOD2 polymorphisms and joint manifestations in CD patients. Peeters et al.73 included 102 patients with CD and identified an association between NOD2 and isolated sacroilits. Seventy eight percent of CD patients with
sacroiliitis carried a NOD2 variant versus 48% of CD patients without sacroiliitis (p=0.01). However, this association could not be confirmed in a recent larger, multicenter cohort of the same group. Several studies found that the NOD2 variants are not involved in the susceptibility to AS. On the other hand, Laukens et al. studied 104 patients with SpA and identified a high prevalence of NOD2 polymorphisms almost similar to the CD population (49%, in their study) in a subgroup of SpA patients with chronic inflammatory gut lesions (38%) compared to SpA patients with acute inflammation and without gut involvement as well as a health control group. A significantly higher frequency of NOD2 mutation carriers was seen in the subpopulation of SpA patients with chronic inflammatory gut lesions than in the control population or the other SpA patients. Thus, NOD2 may play a role in the genetic link between intestinal and joint inflammation.

5.3. HLA-B27 and gut inflammation

Histological studies have demonstrated that SpA patients may have subclinical intestinal inflammation in the absence of gastrointestinal symptoms. The inflammatory changes are divided into an acute type resembling infectious enterocolitis and a chronic inflammation that can evolve to clinically overt CD. Although the exact mechanisms linking the gut and joints in SpA patients are unknown, several hypothesis and animal models for a linkage between gut and joint inflammation in SpA were described.

The animal model of the HLA-B27/human β2-microglobulin transgenic rats showed that these rats developed spontaneously inflammatory intestinal and joint disease. Hammer et al. observed a chronic inflammation involving the stomach and colon in which the colon was most affected and an axial and peripheral arthritis resembling human SpA. Inflammation of gut and/or joint did not occur in germ-free B27 transgenic rats (rats kept in germ-free conditions) but recurred after reintroduction of normal intestinal bacteria. These findings were most convincing evidence for the important role of intestinal bacterial flora in the pathogenesis of B27-associated gut and joint inflammation.

A strong association is observed between HLA-B27 and AS patients in whom more than 90% of patients are HLA-B27 positive. Furthermore, 25–78% of IBD patients with AS are HLA-B27 positive. In contrast, isolated sacroiliitis in CD is unrelated to HLA-B27. Several theories of how HLA-B27 may cause IBD include persistence of bacteria because of altered or defective intracellular killing by HLA-B27 positive cells and misfolding of the HLA-B27 beta-pocket. Another hypothesis proposes that HLA-B27 restricted T lymphocytes can present either bacterial peptides or arthritogenic self-peptides, thus cross reacting with bacterial antigens.

5.4. The role of other proteins

Macrophages expressing the transmembrane protein CD163, which is a member of the scavenger receptor cysteine-rich superfamily that functions in the development and regulation of the immune system, are increased in noninflamed SpA colonic mucosa and in SpA synovium. Demetter et al. found that CD163+ macrophages are increased both in CD and SpA gut mucosa. These observations illustrate that not only T cells but also antigen presenting cells accounts for the relationship between joint and gut inflammation.

Demetter et al. observed an upregulation of E-cadherin, a transmembrane glycoprotein which mediates intercellular adhesion of epithelial cells, and an upregulation of its associated catenins in gut mucosa in IBD. This upregulation was detectable in acute as well as in chronic subclinical gut inflammation in SpA. E-cadherin is also a ligand for the αEβ7 integrin, which is upregulated in colonic mucosa in CD and AS patients and in inflamed synovial tissue in SpA patients. These findings may suggest that these upregulations may play a role in the pathogenesis of IBD or SpA, or both.

Statements

- Activated intestinal lymphocytes in IBD patients adhere to inflamed synovial vessels were VAP-1 supports the binding of all leukocytes.
- NOD2 does not have a clear association with arthropathy in IBD patients.
- HLA-B27 carriers and AS in IBD patients are associated.

6. Treatment

6.1. Peripheral arthropathies

Few studies have been published on the treatment options of arthropathies in IBD patients.

Type 1 peripheral arthritis mostly occurs during exacerbations of IBD activity and therefore, treatment of active intestinal disease should be the main focus. Type 2 arthritis follow a course independent of the activity of IBD and the treatment options are derived from the therapy of axial arthritis and includes non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase (COX)-2 inhibitors and analgesics, physiotherapy and local steroid injection into the worst-affected joints may be considered. Some studies suggest an association between NSAIDs and exacerbations of IBD but data have been conflicting and NSAIDs have been used by many gastroenterologists to good effect with limited risk of exacerbating CD or UC. So, no clear evidence exists in an association between NSAIDs and IBD exacerbations. To clear this topic further study should be needed.

Sandborn et al. performed a placebo controlled pilot trial to evaluate the safety of the COX-2 inhibitor celecoxib in UC patients and concluded that short-term treatment with celecoxib was not associated with a greater clinical and endoscopic relapse rate than placebo. Some small studies showed that COX-2 inhibitors in the treatment of peripheral arthritis and arthralgia in IBD patients was safe and had a beneficial effect.

6.2. Axial arthropathies

NSAIDs are the first line drug treatment for AS patients and effective in relief of spinal and peripheral pain and improvement of spinal mobility. In IBD patients with AS a selective COX-2 inhibitor could be used. According to the 'ASAS/EULAR
6.3. Arthropathies and anti-TNF-α therapy

The TNF-α inhibitors infliximab, etanercept and adalimumab are effective for spinal pain, improvement of spinal function, as well as peripheral joint pain and swelling in SpA patients. The ASAS/EULAR group recommended that anti-TNF-α treatment should be given to AS patients with axial and peripheral symptoms (arthritis and enthesitis) with persistently high disease activity despite conventional treatment. The effect of infliximab on mucosal inflammation in CD and UC has been well established and infliximab has been shown to be efficacious in the treatment of both axial and peripheral arthropathy in SpA. The results of studies published about the treatment of arthropathy in IBD patients with infliximab are encouraging. These studies showed clinical improvement in the severity of pain, duration of morning stiffness, and tender joint count in peripheral arthritis, enthesitis, arthralgia, isolated sacroiliitis and/or AS in active and inactive CD. Infliximab also improved gastrointestinal symptoms and was well tolerated. The results of these studies suggest a possible role of infliximab in the treatment of peripheral as well as axial arthropathy in IBD patients.

Etanercept is well tolerated and efficacious in the treatment of joint manifestations in SpA and CD patients but not in the treatment of CD colitis. Marzo et al. reported an improvement in articular symptoms, but the CD colitis persisted or flared in two patients. Adalimumab is effective in reducing joint symptoms in AS patients resulting in an improvement of the physical function and quality of life. In CD patients adalimumab is also effective and well tolerated but no studies have been published about the effectiveness of adalimumab on arthropathies in IBD patients.

Statements

- Treatment of active intestinal disease should be the main focus.
- COX-2 inhibitors should be given to reduce pain of peripheral arthritis, arthralgia and axial arthritis in IBD patients.
- Anti-TNF-α therapy may be considered to CD patients with persistently high articular activity (axial and/or peripheral).

7. Conclusion

Arthropathies in IBD are clinically divided into peripheral and axial involvement and may be classified as one of the SpA. Peripheral arthropathy and IBP can be diagnosed clinically, but diagnosis of isolated sacroilitis is based on imaging techniques and diagnosis of AS is based on the combination of clinical features and imaging. Unfortunately, there is no reliable laboratory test that can be used as a diagnostic tool in the management or diagnosis of these arthropathies. Joint symptoms in IBD represent a major medical problem in these patients with a worse health related quality of life compared with IBD patients without joint symptoms. Treatment of active intestinal disease should be the main focus for peripheral arthritis type 1 and standard treatment for peripheral arthropathy unrelated to exacerbations of the bowel activity and axial arthropathy includes NSAIDs/COX-2 inhibitors. Anti-TNF-α treatment may be given to patients with persistently high disease activity despite conventional treatments. A close relationship between joint and gut inflammation has been confirmed by several studies but the exact mechanism of the link between arthropathies and IBD is still unknown. Immunologic and genetic factors are thought to play a role. Future studies are needed to understand the pathogenesis of joint manifestations in IBD patients.

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Statement of authorship:

LB collected data and wrote the manuscript. DvdH provided significant advice and revised the manuscript critically for important intellectual content. TH provided significant advice and revised the manuscript critically for important intellectual content. HF drafted the manuscript and revised the manuscript critically for important intellectual content.

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References


