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TOPIC HIGHLIGHT

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Non-invasive investigation in patients with inflammatory joint disease

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Abstract

Gut inflammation can occur in 30%-60% of patients with spondyloarthropathies. However, the presence of such gut inflammation is underestimated, only 27% of patients with histological evidence of gut inflammation have intestinal symptoms, but subclinical gut inflammation is documented in two-thirds of patients with inflammatory joint disease. There are common genetic and immunological mechanisms behind concomitant inflammation in the joints and intestinal tract. A number of blood tests, e.g. erythrocyte sedimentation rate, orosomucoid, C-reactive protein, and white cell and platelet counts, are probably the most commonly used laboratory markers of inflammatory disease, however, these tests are difficult to interpret in arthropathies associated with gut inflammation, since any increases in their blood levels might be attributable to either the joint disease or to gut inflammation. Consequently, it would be useful to have a marker capable of separately identifying gut inflammation. Fecal proteins, which are indirect markers of neutrophil migration in the gut wall, and intestinal permeability, seem to be ideal for monitoring intestinal inflammation: they are easy to measure non-invasively and are specific for intestinal disease in the absence of gastrointestinal infections. Alongside the traditional markers for characterizing intestinal inflammation, there are also antibodies, in all probability generated by the immune response to microbial antigens and auto-antigens, which have proved useful in establishing the diagnosis and assessing the severity of the condition, as well as the prognosis and the risk of complications. In short, non-invasive investigations on the gut in patients with rheumatic disease may be useful in clinical practice for a preliminary assessment of patients with suspected intestinal disease.

Key words: Biochemical markers; Fecal markers; Inflammatory bowel disease; Intestinal permeability; Serological markers; Spondyloarthropathies

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INTRODUCTION

Gut lesions are relatively common in patients with rheumatic disease and approximately 30%-60% patients with spondyloarthropathies have occult intestinal inflammation, which may be related to their ingestion of non-steroidal anti-inflammatory drugs or associated with their rheumatic disease.

Spondyloarthropathies form a group of chronic autoimmune disorders of the joints which include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), and undifferentiated spondyloarthropathies. The prevalence of gut inflammation in ankylosing spondylitis is higher among patients with associated peripheral arthritis than in those with axial involvement alone[1].

Gut inflammation has also been recorded in other spondyloarthropathies. In juvenile chronic arthritis, for instance, when colonoscopy with biopsies of the colonic mucosa and terminal ileum was performed in 12 patients less than 16 years of age, inflammation was observed in 9 patients (75%); gut inflammation could have a

role in the pathogenesis of the disease and persistent synovitis[2].

Two histological types of gut inflammation can be distinguished in spondyloarthropathies, i.e. acute and chronic, based on their morphological characteristics, not on the time of onset or duration of the disease[3]. The acute type resembles acute bacterial enterocolitis, with a well-preserved mucosal architecture. The chronic type resembles chronic ileocolitis and is generally indistinguishable from Crohn's disease, with a clearly disrupted mucosal architecture. While acute lesions are mainly seen in patients with reactive arthritis, chronic lesions are more prevalent in undifferentiated spondyloarthropathies and ankylosing spondylitis[4].

In a prospective study on 123 patients with spondyloarthropathies who initially underwent endoscopy, intestinal evolution was evaluated by ileocolonoscopy and an evolution to IBD was recorded in 7% of these patients[5].

Despite the high frequency of gut lesions in patients with joint diseases, only a few patients are symptomatic. In a series described by Cuvelier *et al*[3], only 27% of patients with histological gut inflammation had intestinal symptoms.

Non-invasive laboratory tests might therefore help to identify rheumatic disease patients with gastrointestinal symptoms who need further investigation. It would be helpful to have inexpensive and manageable tests to facilitate this selection.

GUT-RELATED GENETIC POLYMORPHISMS

There is clinical evidence of a correlation between gut and joint inflammation and the gut could have an important pathogenic role. Remission of joint inflammation has been associated with the disappearance of gut inflammation, and remission of persistent joint inflammation with the disappearance of persistent gut inflammation[4]. Ankylosing spondylitis affects 3%-10% of patients with IBD and is thought to have a genetic origin in these patients that differs from that of "classic" ankylosing spondylitis: while 90% of patients with "classic" ankylosing spondylitis have the human leukocyte antigen B27 phenotype, its prevalence drops to 30% in patients with ankylosing spondylitis associated with Crohn's disease. Polymorphisms of the CARD15 gene may act as a genetic trigger because 78% of patients with Crohn's disease and symptomatic or asymptomatic sacroileitis carry at least one mutation, as opposed to 48% of control patients with Crohn's disease alone[6]. Laukens *et al* confirmed a similar association, finding CARD15 variants in 42% of patients with spondyloarthropathy and asymptomatic gut inflammation, compared with 7% of patients with normal gut histology[7].

In a previous study, the frequency of HLA-Bw62 was found to be very high in patients with reactive arthritis and in those with active ankylosing spondylitis and Crohn-like lesions on gut biopsy[8].

BLOOD MARKERS

A number of proteins are up- or down-regulated in the acute phase of inflammation, and gut inflammation is associated with an acute-phase reaction and the migration of leucocytes to the gut lumen. Several blood tests are used to detect inflammation, however, these tests are unable to discriminate between inflamed joints and inflamed gut[9]. In a study on children with spondyloarthropathies, erythrocyte sedimentation rate (ESR) showed 63% sensitivity and 44% specificity in detecting gut inflammation[10]. Serum levels of human cartilage glycoprotein 39 (also called YKL-40) were recently found to be higher than normal in patients with IBD. More than 60% of Crohn's disease patients with extraintestinal manifestations have high serum YKL-40, as opposed to only 3% of ulcerative colitis patients[11]. We found significantly higher serum levels of YKL-40 in IBD patients with arthropathies than in those without arthropathies or controls ($P < 0.001$ and $P < 0.01$, respectively). The level of this protein also correlates with the number of joints involved, suggesting that this substance could be used as a disease activity marker in arthritis associated with IBD[12].

FECAL MARKERS

As serum markers may increase in various conditions, fecal markers might be more specific for gut inflammation. Barabino *et al*[10] compared a number of non-invasive tests for diagnosing intestinal inflammation in children with spondyloarthropathies. Forty-two children with IBD or rheumatologic manifestations associated with gastrointestinal symptoms were investigated by 99mTechnetium-HMPAO labeled white cell scanning, abdominal ultrasound, ESR, fecal occult blood and fecal alpha 1-antitrypsin tests. 99mTechnetium-HMPAO labeled white cell scanning was shown to be the most sensitive (85%) and specific (100%) in detecting gut inflammation. White cell scanning combined with the measurement of fecal excretion of labeled white cells was able to quantify inflammation accurately in an additional study: following intravenous administration of 111In-labelled leukocytes, fecal 111In granulocyte excretion correlated significantly with Crohn's disease activity index ($P < 0.001$), C-reactive protein (CRP) ($P < 0.001$) and ESR ($P < 0.001$)[13]. This technique is expensive and time-consuming, however, and involves the use of radiation. Moreover, leukocytes do not survive for long periods in feces due to bacterial degradation[14]. As an alternative, fecal leukocytes can be seen under the microscope, but again, such an evaluation is not practicable because it has to be carried out on fresh stools. Some leukocyte proteins, such as lactoferrin and calprotectin, are more durable and can be used as surrogate markers of the presence of leukocytes in stools. Fecal calprotectin levels have been shown to correlate with intestinal inflammation, as assessed by 111Indium-labeled leukocyte studies on 4-d-old fecal samples and the correlation was maintained, even when

a single stool specimen was examined[15,16].

A number of neutrophil-derived proteins have been studied in stools, including fecal calprotectin, lactoferrin, lysozyme, elastase and myeloperoxidase[17,18]. Experience with the analysis of fecal proteins has been gained mainly with calprotectin and lactoferrin. Calprotectin represents 60% of the cytosolic proteins in granulocytes, and is released from cells during cell activation or death, while lactoferrin is a component of the granules in the neutrophilic granulocytes, so their presence in feces is presumably directly proportional to neutrophil migration in the gut lumen[19,20]. Both calprotectin and lactoferrin are stable in stools for more than 7 d at room temperature[19,20].

Determining intestinal inflammation by means of fecal markers is of considerable interest to clinicians in various settings, e.g. to discriminate between patients with organic and functional processes, to monitor disease activity and response to treatment, and to predict relapses in IBD. Both calprotectin and lactoferrin have been found to correlate with intestinal inflammation in studies on patients undergoing colonoscopy for gastrointestinal symptoms or surveillance[21,22].

In a recent study, calprotectin and lactoferrin appeared to be equally recommendable as inflammatory disease markers in patients with lower gastrointestinal symptoms and both reflected inflammatory activity in IBD[23].

Fecal calprotectin and lactoferrin are equally useful in assessing disease activity: calprotectin correlated with endoscopic findings, lactoferrin with histology[23,24].

Fecal calprotectin also proved useful in predicting relapses in patients in clinical remission, probably reflecting subclinical activity. Tibble *et al*[25] found that fecal calprotectin levels greater than 50 μg/g were a sensitive and specific predictor of relapse in the short term in both ulcerative colitis and Crohn's disease (with 90% sensitivity and 83% specificity). More recently, Costa *et al*[26] found that ulcerative colitis patients with fecal calprotectin levels higher than 150 μg/g had a 14-fold relapse risk, while Crohn's disease patients had only a two-fold risk of relapse, which was not statistically significant. D'Incà *et al*[27] observed that calprotectin levels beyond 130 mg/kg correlated significantly with the probability of relapse in ulcerative colitis patients ($P = 0.000$) and colonic Crohn's disease patients ($P = 0.02$), but not in patients with ileal or ileocolonic disease.

INTESTINAL PERMEABILITY

Permeability refers to the property of a membrane that enables a solute to pass through it by unmediated diffusion due to the membrane's structure, the physical and chemical properties of the solute, and its interaction with the medium or solvent. Intestinal permeability is assessed non-invasively *in vivo* by measuring the urinary excretion of orally administered hydrosoluble, non-toxic and non-degradable probes, e.g. lactulose/mannitol, lactulose/rhamnose, ^{51}Cr-EDTA/rhamnose, or D-xylose.

Bjarnason *et al* postulated that a greater intestinal permeability to toxic "non-absorbable" compounds might be responsible for some of the extraintestinal tissue damage common in alcoholic patients[28]. An altered intestinal permeability may also represent the primary defect in patients with arthropathy. An increased antigenic load could result from an altered intestinal permeability, since higher levels of antibodies to *Klebsiella pneumoniae* have been found in the serum of patients with ankylosing spondylitis, rheumatoid arthritis and IBD[29]. Morris *et al*[30] found that small intestinal permeability increased in patients with ankylosing spondylitis taking non-steroidal anti-inflammatory drugs, suggesting that the increased permeability was probably not a primary mucosal lesion, but caused by the medication. De Vos *et al*[31] found both acute and chronic inflammation at the macroscopic (30%) and histological (61%) level in the terminal ileum of patients who were seronegative for arthropathy and were not taking non-steroidal anti-inflammatory drugs. Chronic inflammation predominated in ankylosing spondylitis patients, resembling Crohn's disease in one third of patients. Mielants *et al*[32,33] observed a greater gut permeability in rheumatic patients irrespective of whether they were taking non-steroidal anti-inflammatory drugs, indicating that the disrupted permeability is disease-related.

Altered gut permeability was also seen in juvenile chronic arthritides, which are frequently associated with IBD, despite the use of non-steroidal anti-inflammatory drugs ($P = 0.210$), disease activity ($P = 0.24$) and type of disease ($P = 0.28$)[34].

The same findings have been reported in various intestinal conditions, such as celiac disease[35], IBD[36], infectious gastroenteritis[37], and food intolerance or allergy[38,39]. We had the opportunity to study 261 consecutive patients referred with chronic diarrhea and found that the intestinal permeability test and CRP levels were independent predictors of the final diagnosis of an underlying organic small bowel disease. The test correctly identified the presence of organic disease in 80% of patients[40].

The permeability test is used in Crohn's disease to monitor disease activity and as a predictor of relapse in quiescent Crohn's disease. In active Crohn's enteritis, 95% of patients have an increased intestinal permeability, while in Crohn's colitis this is true of about 50% of patients[41]. Studies in patients with Crohn's disease in remission have shown that an increased intestinal permeability can pinpoint those at significant risk of disease relapse within the next few months[42,43].

SEROLOGICAL MARKERS

Serological tests focus on several antibodies, the most widely used being perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA). p-ANCA were first described in ulcerative colitis patients in 1990, but the exact epitope remains unknown[44,45]. ASCA are directed against the cellular wall of baking yeast.

The specificity of both markers is very high, but their sensitivity is rather low and these tests are consequently

not suitable for screening purposes[46]. Combining the two (p-ANCA and ASCA) may be helpful, however, in the differential diagnosis between ulcerative colitis and Crohn's disease the combination of ASCA+/p-ANCA- is characteristic of Crohn's disease, while ASCA-/p-ANCA+ is characteristic of ulcerative colitis, with a sensitivity that ranges from 30%-64%, a specificity beyond 90% and a positive predictive value between 77% and 96%[47-49]. ASCA positivity has been related to disease severity[50], the risk of having to undergo surgery[51], and an ileal and/or right colonic localization of the disease[48,52].

The recent finding that p-ANCA and ASCA can be found in 25%-30% of patients some years before any IBD is diagnosed has shed some light on its pathogenesis[53].

Two studies documented a higher prevalence of ASCA IgA positivity in ankylosing spondylitis[54,55], adding proof to the conviction that spondyloarthropathies and IBD are immunologically related. Additional serum biomarkers include antibodies against outer membrane porin C (Anti-OmpC), the *Pseudomonas fluorescens* bacterial sequence I2 (anti-I2), bacterial flagellin (antiCBir1) and the anti-glycan antibodies, i.e. anti-chitobioside IgA (ACCA), anti-laminaribioside IgG (ALCA) and anti-mannobioside (AMCA)[46,56-58]. Although the data from independent studies vary, combining more than one serological marker has been shown to add clinical value, particularly in predicting a complicated disease behavior, including strictures, fistulas and the need for surgery.

CONCLUSION

Patients with spondyloarthropathies often have inflammation in the gut, especially in the terminal ileum, although only 30% of the patients involved have clinical symptoms.

The frequency of gastrointestinal disease remains poorly understood and should be investigated in all patients with chronic spondyloarthropathy. The early diagnosis and treatment of gut inflammation may make it unnecessary to use drugs that can damage the intestinal mucosa[59-61].

Biochemical markers are useful in managing gut inflammation, representing a valuable aid in the diagnosis of inflammatory processes and the evaluation of their prognosis.

The ideal marker should be easy to test, repeatable and inexpensive. Currently used blood markers are non-specific and reflect both joint and intestinal inflammation. The fecal markers calprotectin and lactoferrin, and intestinal permeability are more promising tests, as they have a good specificity for intestinal disorders and are straightforward to perform. This is very important, particularly to pinpoint those patients without intestinal symptoms who need to be selected for further, more invasive investigations, and to avoid medication-related complications.

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