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Extra-intestinal manifestations of IBD involving musculo-skelatal system

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Abstract
Ulcerative colitis is an autoimmune disorder of unknown etiology. Although the large intestine is the major focus of autoimmunity, resulting in chronic diarrhea, that is actually a systemic disease, with numerous extraintestinal manifestations, such as articular involvement. The frequent association of a number of autoimmune diseases in the same patient has been described. However, the coexistence of ulcerative colitis and rheumatoid arthritis is rare. Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are common in both ulcerative colitis (UC) and Crohn's disease (CD). These manifestations can involve nearly any organ system—including the musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal, and pulmonary systems—and can cause a significant challenge to physicians managing IBD patients. Most IBD patients with EIMs have colonic inflammation, although some patients develop EIMs prior to the onset of colonic symptoms. In this paper, we review the major EIMs of IBD and strategies for their management. Thus chronic patients of IBD were analysed for symptoms of Arthritis and a significant number of studied patients had found early –late symptoms of joint problems in this work.

Keywords: Arthritis, joint problems, ulcerative Colotis, Crohn's Disease, BMD

Introduction
Arthritis means inflammation of joints. Inflammation is a body process that can result in pain, swelling, warmth, redness and stiffness. Sometimes inflammation can also affect the bowel. When it does that process is called inflammatory bowel disease (IBD). IBD is actually two separate diseases: Crohn's disease and ulcerative colitis. With proper treatment most people who have these diseases can lead full active lives. Usually the inflammation of joints in IBD lasts only a short time and does not cause permanent deformity. With the bowel symptoms under control through medication and diet the outlook for the joints is excellent. Both men and women are affected equally. The arthritis of IBD can appear at any age but is most common between the ages of 25 and 45.Joint inflammation begins most often when the colon (the large intestine) is involved in the disease process. In adults the arthritis is usually most active when the bowel disease is active. Indeed the amount of bowel disease usually influences the severity of the arthritis. In children the arthritis is not as often associated with increased bowel disease activity. Ulcerative colitis produces inflammation and breakdown along the lining of the colon. Inflammation usually begins in the rectum and extends up the colon. Symptoms may include rectal bleeding abdominal cramping weight loss and fever. The bowel symptoms often occur before the symptoms of arthritis. When ulcerative colitis is present the arthritis is most likely to occur if there is severe bleeding or if the area around the anus is inflamed. When only the rectum is involved the chance of getting arthritis is less. One or more joints may be affected and the symptoms often move from joint to joint. The hips knees and ankles are involved most often although any joint may be affected. The joints may be very painful red and hot but these symptoms usually do not result in permanent damage. People with ulcerative colitis can develop another form of arthritis called ankylosing spondylitis, which involves inflammation of the spine. It usually begins around the sacroiliac joints at the bottom of the back. Symptoms of spondylitis generally do not accompany bowel symptoms in ulcerative colitis.
Crohn's disease usually involves either the colon or the ileum the lower small intestine. It may affect both or any part of the digestive tract from the mouth to the rectum. The inflammation involves all layers of the intestinal wall and may lead to scarring and narrowing of the bowel. Fever weight loss and loss of appetite are common symptoms of Crohn's disease. The arthritis of Crohn's disease can occur before after or at the same time as the bowel symptoms. As with ulcerative colitis the large joints such as the knees and ankles are generally affected though not

necessarily on both sides of the body and back pain can result from ankylosing spondylitis. Inflammatory bowel disease (IBD) is an inflammatory disorder of the gastrointestinal (GI) tract that is both chronic and relapsing; it encompasses both Crohn's disease (CD) and ulcerative colitis (UC). In addition to affecting the GI tract, IBD has several extra-intestinal manifestations (EIM), including arthritis, ocular involvement, dermatologic manifestations, pulmonary manifestations, biliary tree complications, anemia, and thromboembolism.

Arthritis is a common EIM in IBD, occurring in approximately 30% of IBD patients. Arthropathy has significant effects on morbidity and quality of life in patients with IBD. Here we review the epidemiology, pathophysiology, clinical manifestations, and treatment of arthropathy associated with IBD. Arthropathy associated with IBD can involve both peripheral and axial joints. IBD associated arthropathy is considered a type of seronegative spondyloarthropathy (SpA). Spondyloarthropathies (which also include Ankylosing Spondylitis (AS), Psoriatic Arthritis, Reactive Arthritis, and Undifferentiated SpA), are characterized by axial and peripheral joint disease with inflammatory features and classically a negative rheumatoid factor. Spondyloarthropathies share a common genetic predisposition, including HLA-B27 association. Extraarticular manifestations such as skin manifestations, dactylitis, enthesopathy, and eye disease can also be seen. IBD-associated arthritis is more akin to AS than to the other subtypes of SpA in that it is more likely to be symmetric and continuous, whereas reactive arthritis or psoriatic arthritis can be asymmetric or have non-continuous lesions within the spine. The European Spondyloarthropathy Study Group criteria (ESSG) are most commonly used for classification of SpA. Orchard *et al*. defined two categories of IBD patients with peripheral arthritis. Type 1 is a pauci/oligo-articular arthritis with swelling and pain of five or fewer joints, particularly affecting large joints in the lower extremities. Type 1 arthritis tends to be acute and self-limiting, and correlates with IBD activity. Joint symptoms can occur prior to the diagnosis of IBD. Type 2 peripheral arthritis has a more poly-articular (affecting greater than five joints), symmetrical distribution, affecting upper limbs predominantly (MCPs commonly affected). Type 2 peripheral arthritis may be chronic and is less likely to parallel the IBD activity. In both types, peripheral arthritis tends to be non-deforming and non-erosive. The possibility of an alternative diagnosis, such as Rheumatoid Arthritis or PsA should be considered in IBD patients who develop erosive arthritis.

Other musculoskeletal manifestations in IBD include enthesitis (inflammation at tendon insertion site), dactylitis (sausage like swelling of digit), and arthralgia (joint pain with lack of inflammation). Complications of IBD and its treatment such as septic arthritis or osteonecrosis should also be considered in the differential of joint pain occurring in the IBD patient, particularly in the setting of mono or oligoarticular arthritis.Lastly, many patients will note diffuse pain that is due to an underlying myofascial pain syndrome. This is seen in other inflammatory disorders as well, for example in 4% to 17% of affected patients with RA or AS. Fibromyalgia or chronic widespread pain has been reported in approximately 10% to 30% of patients with IBD.

Prevalence: Nearly 4 million individuals worldwide are affected with inflammatory bowel disease and approximately 1.4 million of these cases occur in the country, the prevalence of CD and UC among adults is 201 and 238 per 100,000, respectively. Arthropathy is the most common EIM seen in IBD, with reported overall prevalence of 17–39%. Classification or diagnostic criteria, if specified, are included. Studies which did not provide sufficient data to assess methodology, incidence or prevalence, or appropriate diagnosis were excluded. The reported prevalence is widely variable between studies; discrepancies may be due to differences in study methods for patient selection or diagnostic criteria for arthropathy. While an exam by a rheumatologist was conducted in a majority of the studies, this was often done only in selected patients who were overtly symptomatic on visit to a gastroenterologist, those who self reported arthritis on a questionnaire, or who had diagnosis of arthritis on review of medical records. Considering these studies only, a more accurate overall prevalence may be 31.5–39%. The prevalence of arthritis may also be underestimated due to the transient nature of oligoarticular peripheral arthritis or the response of arthritis to steroids given for IBD flares. Many of the studies were cross-sectional. As extraintestinal manifestations develop over time, the true incidence or prevalence cannot be estimated from those analyses.

Approximately 60—70% of the arthritis seen in IBD patients is peripheral arthritis, in which the large joints are affected, and this arthritis is typically an oligoarthritis, meaning that fewer than 5 joints are affected. The most commonly affected joints are the knees, ankles, wrists, elbows, and hips. A smaller proportion of IBD patients have symmetrical polyarthritis, which has a presentation similar to that of rheumatoid arthritis; these patients can develop inflammation in any joints, but typically the small joints of the hands are affected. Finally, 1—6% of all IBD patients develop ankylosing spondylitis, which is a progressive inflammatory arthropathy affecting the sacroiliac joints and the spine. These patients develop gradual fusion of the spine over a period of time. While large joint arthritis is nearly always associated with active IBD, ankylosing spondylitis and small joint polyarthritis can flare up independently of the patient's IBD.

The arthritis that occurs in IBD patients is very unlike rheumatoid arthritis. Patients who have rheumatoid arthritis have an erosive and deforming arthropathy that gradually destroys the joints, and a number of these patients require joint replacement surgery. In contrast, the arthritis associated with IBD is not erosive or deforming and should do no long-term damage to the joints. In general, IBD patients with peripheral arthritis present with acute, hot, swollen joints, and with the large joint arthritis, patients often present with pain and swelling that migrate from joint to joint. Compared to large joint arthritis, the peripheral polyarthritis tends to be more persistent, lasting for 1—2 years, and affecting the same joints consistently.

In some cases, clinicians may mistake large joint arthritis for reactive arthritis, which is a type of arthritis that can develop in response to infections—for example, *Shigella* or *Yersinia* infections in the gut or chlamydial infections of the genitourinary system. Diagnosis can sometimes be quite confusing in these cases, as reactive arthritis in the context of a gut infection can very closely mimic the arthritis that occurs in patients with IBD. In patients known to have IBD, a presentation with diarrhea and arthritis could be due to reactive arthritis secondary to a gut infection, or it could be a flare of the IBD associated with arthritis. For patients not known to have IBD, this clinical presentation can be the first presentation of IBD, as joint problems are the first symptom

of the disease in some IBD patients.

The patterns of arthritis are actually the same in CD and UC; however, there appears to be a slightly greater prevalence of arthritis in CD compared to UC. Patients who have CD that affects the large bowel probably have the most arthritis. Some evidence suggests that the most important areas of the gut in terms of the development of arthritis are the right-hand side of the colon and the bottom of the small bowel, but this association has not been conclusively demonstrated.

The development of arthritis in these patients definitely involves a genetic component, which probably makes patients susceptible to luminal microbiota that can trigger arthritis. The arthritis associated with IBD is classified as a seronegative spondyloarthropathy; all the conditions in this group involve the development of arthritis without the presence of autoantibodies, and all these conditions are associated with an increased risk of developing ankylosing spondylitis. Ankylosing spon-dylitis is known to be strongly associated with *HLA-B27*, which is a particular variant of an *HLA* gene that controls the immune response, and peripheral arthritis in IBD patients is also associated with *HLA-B27*, although less strongly; this common association probably accounts for the increase in ankylosing spondylitis among patients with seronegative spondyloarthropathy. However, peripheral arthritis in IBD patients has an even stronger association with a rare *HLA* allele called *HLA-DR103*. This allele is present in approximately 35% of patients with large joint arthritis and in up to 65% of patients who have more than 1 episode of large joint arthritis. In comparison, this allele occurs in only 1—3% of the general population. How this genetic association results in arthritis among IBD patients is largely speculation. My hypothesis is that episodic bouts of arthritis are triggered by the combination of a leaky, inflamed gut, which is found in IBD, plus a genetic susceptibility to certain bacteria that patients may encounter. This susceptibility is determined by the *HLA* genes (and possibly other genes) that patients have inherited, and it allows an uncontrolled inflammatory response to develop, specifically targeting the joints.

Collectively, these are called, and they can occur prior to, in conjunction with, or subsequent to active bowel disease. The overall prevalence of any extraintestinal manifestation in IBD patients ranges from 21%-40%.In most large studies of IBD, the prevalence of extraintestinal manifestations is higher in Crohn's disease compared with ulcerative colitis. There may also be racial differences in prevalence, with blacks having a higher risk for eye and joint manifestations, and Hispanics having a higher risk for skin manifestations, compared with whites. Musculoskeletal Manifestations- The peripheral and axial musculoskeletal syndromes associated with IBD are considered part of the seronegative spondyloarthropathies, and are seen in approximately 30% of patients with IBD Peripheral arthritis associated with IBD is typically classified into types 1 and 2.Type 1 disease affects fewer than 5 large joints, is acute and is self-limited, and is usually associated with active disease in the bowel. Type 2 disease typically chronic, affects 5 or more small joints, is symmetrical, and is not associated with the activity of the bowel disease. Axial arthropathies, including sacroiliitis and ankylosing spondylitis, are also associated with IBD but are usually independent of disease activity. Ankylosing spondylitis and sacroiliitis involve inflammation of the spine and sacroiliac joints, respectively. They present as pain and stiffness in the low back that is worse in the morning and relieved with exercise.

Etiopathology: The link between gut and joint inflammation in IBD is not fully understood but has been extensively studied. Interestingly, patients with all subsets of SpA have demonstrated subclinical evidence of gut inflammation, and 7% of patients with any SpA may go on to develop overt IBD. Prospective serial ileocolonoscopy studies have demonstrated a relationship between coincident gut and joint inflammation in SpA, though relative severities were not commented on. Peripheral arthritis has also been correlated with increased gut inflammation in patients without IBD, and remission of arthritis was accompanied by normalization of gut mucosa. Two major theories to explain development of arthritis in the setting of IBD involve gut bacteria and migration of gut lymphocytes to the joint, but neither have been fully developed. In the first, the HLA-B27/human β2 microglobulin transgenic rat model of SpA like disease, a germ free environment prevents the development of gut and joint disease, suggesting bacterial exposure is necessary for the development of SpA in the proper genetic background.This model does not explain the co-localization of inflammation to the synovium and gut or identify the specific bacterial antigens which may incite inflammation.

In the second theory, lymphocyte trafficking to various tissues is dependent on various adhesion molecules and receptors. For gut homing, α4β7 and αEβ7 integrins and MadCAM-1 mucosal vascular receptor are important. Binding of intestinal lymphocytes to synovium from in vitro studies seems to be dependent on other adhesion molecules such as vascular adhesion protein-1 (VAP-1). Lymphocytes from the gut may migrate to the synovium, leading to inflammatory arthritis. Identical T cell clones have been indentified in synovium and gut mucosa from a patient with SpA. In addition to lymphocytes, macrophages expressing the scavenger receptor CD163 have been found in gut mucosa from patients with CD and SpA as well as in synovium. It is possible that these cells could also migrate from the gut to the joint, as in vitro they can bind to synovial tissue vessels. While these models exhibit the importance of lymphocyte and macrophage trafficking and explain how effector cells can co-localize to the gut and synovium, the inciting antigen or immune trigger remains unclear. A novel mechanism proposed by studies in the TNF overexpressing $TNF^{\Delta ARE}$ mouse model of SpA-like disease has suggested that mesenchymal cells in the gut and joints may be targets for TNF mediated inflammation. This suggests another cell type linking intestinal and joint pathologies. Systems Affected-

Sites	Extra-intestinal manifestations
Musculoskeletal system	• Arthritis: colitic type, ankylosing spondylitis, isolated joint involvement • Hypertrophic osteoarthropathy: clubbing, periostitis • Miscellaneous manifestations: osteoporosis, aseptic necrosis, polymyositis
Dermatologic and oral systems	• Reactive lesions: erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizingvasculitis • Specific lesions: fissures, fistulas, oral Crohn's disease, drug rashes • Nutritional deficiencies: acrodermatitis enteropathica, purpura, glossitis, hair loss, brittle nails

	• Associated diseases: vitiligo, psoriasis, amyloidosis
Hepatopancreatobiliary system	• Primary sclerosing cholangitis, bile-duct carcinoma • Associated inflammation: autoimmune chronic active hepatitis, pericholangitis, portal fibrosis, cirrhosis, granulomatous disease • Metabolic manifestations: fatty liver, gallstones associated with ileal Crohn's disease
Ocular system	• Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease
Metabolic system	• Growth retardation in children and adolescents, delayed sexual maturation
Renal system	• Calcium oxalate stones

EIMs are seen in 25–40% of IBD patients. Inflammatory manifestations of the skin, eyes, liver, and joints are considered primary manifestations. If secondary effects of disease activity are also considered, nearly 100% of IBD patients have an abnormality outside of the gastrointestinal tract lumen. Twenty-five percent of IBD patients have more than 1 EIM. The development of 1 EIM appears to increase the risk of developing a second EIM. Few studies have specifically examined how frequently an EIM is a patient's presenting symptom or is present at the time of diagnosis versus occurring later in the disease course. In a retrospective study of 448 IBD patients, Aghazadeh and associates showed that 31.4% of UC patients and 40.4% of CD patients had 1 of the 5 major manifestations; a smaller percentage of patients had more than 1 major EIM. Limited data have shown that approximately one third of patients will develop symptomatic primary sclerosing cholangitis (PSC) prior to a diagnosis of IBD. Based on several small studies, 10–30% of patients with arthritis related to IBD will have arthritic symptoms prior to IBD diagnosis.

Musculoskeletal pain occurs in 9–53% of IBD patients and is considered the most common EIM. The differential diagnosis of this condition includes articular, periarticular, and muscular involvement; osteoporosis and related fractures; and fibromyalgia.Arthritis can affect the spine, sacroiliac joint, peripheral joints, or a combination of these sites. Classically, inflammatory arthritis is defined by pain, an increase in local temperature, and joint swelling with or without effusion, leading to decreased joint mobility. Associated peri-articular features include tendonitis, clubbing, periostitis, and granulomatous lesions of the joint and bone. Inflammatory arthritis can be differentiated from osteoarthritis by morning stiffness and improvement with ambulation.

Hypothesis: Based on the above mentioned studies and facts we designed a hypothesis that The Irritable Bowel Syndrome has some extra-intestinal effects specially related to poor bone health.

Methodology: In this case-control study I have contacted chronic patients of IBD, especially those having some joint pain related problems. After taking their medical history and demographic data, their biochemistry and imaging was done in relevant parameters of IBD. The family members, who are age matched with victims of IBD (subjects) with matched genetic profile with subjects were selected as controls.

Subjects: Chronic patients of Irritable Bowel Syndrome were contacted personally and also by contacting Dr Devendra Singh, Gastroentologist, Bilaspur. After completing formalities related to medical ethics –taking permission from all subjects for analysis the observation were made. The age range of the subjects were 28-49 years, total number was 22, 18 were male, rest were females in experimental group and 22 controls were picked from the families of subjects.

Observations: The history taken by the doctor is the most important part of the diagnosis. Certain information--such as the way the arthritis began the specific joints involved and the relationship between joint and bowel symptoms--is very helpful for diagnosis. The appearance of the joints their range of motion and pain or tenderness during the physical examination are also important. Usually X-rays of the joints are normal unless the joints of the spine are affected. Then damage is visible in X-rays. A blood test for the presence of a substance called HLA-B27 in the blood cells is sometimes helpful in diagnosing ankylosing spondylitis. This substance is an inherited factor present in a much higher frequency among people who have IBD and spondylitis than in the normal population. blood tests for markers of inflammation or genes that are common in people with IBD and arthritis

Biochemical Parameters taken-

- Anemia- Microcytic Hypochronic Anaemia was tested, the hematology was done by using Hematology chamber.
- Bleeding from rectum was tested for Malena condition, Benzidine test was done.
- Weight loss was tested by common digital weighing machine and by taking height, BMI was also calculated.
- A family history of digestive diseases, such as celiac disease, colon cancer, or inflammatory bowel disease was collected.
- Medicines, which were taken /were taking during study was noted
- Recent infections
- Stressful events related to the start of subject’s symptoms
- Food history was taken
- Checks for abdominal bloating by using stethoscope
- Taps on subject’s abdomen checking for tenderness or pain
- Presence of fever was noted
- 6 patents were undergone for hydrogen breath test to check for small intestinal bacterial overgrowth or problems digesting certain carbohydrates, such as lactose intolerance on their own expenses
- Upper GI endoscopy with a biopsy to check for celiac disease –this medical procedure was followed by all subjects
- Colonoscopy to check for conditions such as colon cancer or inflammatory bowel disease was done in 16 subjects
- CBC (complete blood count) to check for anemia; bleeding caused by IBD and similar conditions can lead to anemia
- Fecal occult blood test or fecal immunochemical test to look for blood in the stool
- CRP (C-reactive protein) to look for inflammation; this test may also be used later to help distinguish IBD from irritable bowel syndrome (IBS) and may be used after diagnosis to monitor the course of the disease.
- ESR (erythrocyte sedimentation rate) was done to detect

inflammation.

- Serum Albumin gm % was tested by using Biochemistry Autoanlayser Star 100, by using Kit of Span diagnostics.
- Some parameters of LFT (Liver Function Tests) were also taken as Hepatic profile is also disturbed in IBD, by using Biochemistry Auto-analyser Star 21.-
- Aspartate aminotransferase (AST or SGOT)
- Alanine aminotransferase (ALT or SGPT)
- Alkaline phosphatase, 5' nucleotidase,
- Gamma-glutamyl transpeptidase (GGT)
- LDH (Lactate dehydrogenase)

The AST and ALT readings in such cases are usually between twice the upper limits of normal and several hundred units/liter. One of the most common causes of mild to moderate elevations of these liver tests is a condition referred to as IBD.

Observations

Sr No	Parameters	Patients Mean Values	Participated	Controls Mean Values	Participated	Significant Difference
1	ESR	89	30	26	30	2.004
2	Serum Albumin	1.044 ng/mL	30	3.9 ng/mL	30	8.713
3	C- reactive protein (CRP)	3.1 mg/L	30	0.7 mg/L	30	6.002
4	Aspartate Amino transferase (AST or SGOT)	132 Units /L	30	18.3 units /L	30	1.322
4	Alanine Amino transferase (ALT or SGPT)	278 Units/L	30	33 /L	30	8.066
5	Alkaline phosphatase	249 U/L	30	63 U/L.	30	1.81
6	gamma-glutamyl transpeptidase (GGT)	87 U/L	30	19 U/L.	30	4.41
7	LDH (Lactate dehydrogenase)	244 U/L	30	119 U/L	30	1.005
8	Prothrombin time	34 Seconds	30	11.2 seconds.	30	6.93
9	Serum Bilirubin	5.1 mg/dL	30	0.09 mg/dL	30	1.90
10	Total Platelet Count	112,000 /µL	30	223,000 /µL	30	2.09
11	CT	computed tomography showed Inflammatory lesions in Colon	15	Not shown	15	--
12	Ultra sound	Grade -3 to 4 lesions	11	Normal GIT	9	--
13	MRI Of Knee and Shoulder	Decaying was observed	3	Normal MRI	3	--
14	BMD	51% Density	13	92% normal density	13	--
15	Melina	83% have	30	2%	30	--
16	Upper GI X-ray (barium)	Multiple intestinal abbesses	30	4%	30	--

Conclusion: The present work suggests that Inflammatory Bowel Disease is an etiological factor for joint-bone diseases. The Liver and hematology of the victims are also affected as observed in biochemical profile of the subjects. The work doesn't support the hypothesis of genetically involvement in this relation of IBD and joint-bone problems as the family members of the subjects are safe from IBD. Arthropathy is common in inflammatory bowel disease, with both peripheral and axial musculoskeletal manifestations. Pauciarticular peripheral arthritis may correlate better with intestinal disease than polyarticular arthritis or axial arthritis. The victims also showed poor Bone Mass Density, Higher serum C –Protein level due to inflammation in arthritis, they had frank symptoms of joint pain, redness and swelling in 38% percent of victims. The connection between gut and joint inflammation, and predisposing genetic factors, remain unclear. The biochemical data showed hepatic involvement in IBD as the hepatic enzymatic profile of victims showed all elevated parameters. Imaging can be helpful in identifying axial disease, and MRI can aid in earlier detection of inflammatory spinal and sacroiliac disease as this study also proved diagnostic significance of imaging techniques in this very disease. There are few studies specifically examining the treatment of arthritis in IBD. But the present study supports the previous studies that IBD may be a significant predisposing factor for joint diseases, specially arthritis. A wide community based study is required to conform the findings.

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