Etiopathogenesis of sacroiliitis: implications for assessment and management

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INTRODUCTION

Sacroiliitis is a painful inflammation of the sacroiliac joint which is particularly challenging to diagnose [1]. Sacroiliitis is linked to inflammatory arthritis of the spine. The inflammation may have different causes, including autoimmunity, microtrauma, exercise, and in some cases, infections. Sacroiliitis can also be associated with Crohn’s Disease, inflammatory bowel disease, and osteoarthritis.
Etiopathogenesis of sacroiliitis

The ligaments of the sacroiliac joint include the anterior sacroiliac, intersosseous sacroiliac, posterior sacroiliac, and the extrinsic sacroiliac joint ligaments [9]. A close anatomical relationship exists between the long posterior sacroiliac ligament, the erector spinae muscle, the posterior layer of the thoracolumbar fascia, and part of the sacrotuberosous ligament. The main part of the sacrotuberosous liga-

ment connects the sacrum with the ischial tuberosity [10]. The extrinsic sacroiliac joint ligaments limit the flexion of the sacrum, whereas the intersosseous ligaments run vertically from ilium to sacrum [11]. During pregnancy, there is increased production of relaxin, a hormone involved in loosening ligaments and the symphysis pubis. This enables the wide opening of the pelvic joint during childbirth [12].

The sacroiliac joint can produce pain but its exact innervation is still unclear [13]. Cunningham’s Textbook of Anatomy [14] states that “the sacroiliac joint is supplied: 1) by twigs directly from the sacral plexus and the dorsal ramus of the first two sacral nerves; and 2) by branches from the superior gluteal and obturator nerves” [15]. Holm et al. [16] proposed an innervation model of the sacroiliac joint in which the major innervation of the joint involves the L4-S1 nerve roots. Posterior rami of L4-S3 innervate the posterior side through its lateral branches while the L2-S2 segments innervate the anterior side. Successful attenuation of sacroiliac joint pain has been reported by Patel et al. [17] after neurotomy of the L5 dorsal primary ramus. By this technique, they also found involvement of lateral branches of the dorsal sacral rami from S1-S3 in sacroiliac joint pain. The sacroiliac joints contain myelinated and unmyelinated nerve fibres along with encapsulated endings. The diameter of many axons that innervate the joint is about 0.2-2.5 mm [9]. Axons with these anatomical and physiological properties have been associated with nociception in other areas and may be involved in perception of pain from the sacroiliac joint.

In early life, the sacroiliac joint surfaces are flat or regular. As the body starts moving/walking, load is transmitted to the lower body through the sacroiliac joint. The joint surfaces then lose planar topology and angular orientations arise [5]. An elevated ridge develops along the iliac surface and a depression along the sacral surface. This, in turn, increases joint stability and makes dislocations very rare [18]. With age, the joint space decreases, becomes more irregular and is filled with debris. During aging, there is no fusion of the joint [19]. As the joint fills with debris, it becomes stiffer and does not respond well to trauma. This, along with decreased bone mineral density, predisposes the elderly to stress fractures due to a weakened sacral bone [20]. Various anatomical variants of the sacroiliac joint have been reported by different researchers. Prassopoulos et al. [21] classified anatomic variants as accessory joint, iliosacral complex, bipartite iliac bony plate, crescent-like iliac bony plate, semicircular defects, and ossification centers. All these variants occurred in different patients and each patient’s joint had a distinct appearance.
2. Clinical signs of sacroiliitis

Low back pain is a common clinical manifestation, affecting approximately 70% of people at some stage of their life [22]. Pain in the sacroiliac joint and surrounding structures can present as low back, pelvic, gluteal, or sacral pain in patterns that vary widely. The pain may be described as sensations such as numbness, popping, or clicking pain usually below the beltline. Moreover, it could be referred to the groin [4]. It may be uni- or bi-lateral, though unilateral is four times more frequent than bilateral pain. People that practice sports or do jobs involving unilateral loading of the legs are at higher risk of low back pain [23].

Although a specific cause of chronic low back pain can be identified in about 75% of patients, low back pain is usually considered idiopathic [24]. Dysfunction of the sacroiliac joint is a major source of such pain and may account for as much as 20% of complaints of low back pain in the general population [25]. The pathological conditions causing sacroiliac joint dysfunction are inflammatory and mechanical. The mechanical condition, referred to as sacroiliac joint syndrome, usually emerges from minor subluxations and/or ligamentous strain in the joint, although the exact mechanism is unclear [10]. Sacroiliitis can also be caused by ankylosing spondylitis. Ankylosing spondylitis is characterized by fibrosis and ossification of ligaments and capsules, and primarily affects the spine (100% of cases), intervertebral joints (75%), shoulders (30%), and knees (20%) [26].

1) Diagnosis

Sacroiliitis is difficult to detect. Fractures, tumors, and joint structural alterations can be assessed by pelvic X-ray [27]. Early detection methods include bone scans, but they cannot distinguish mechanical from bacterial septic sacroiliitis [28].

Magnetic resonance imaging (MRI) appears to be useful for evaluating the sacroiliac joints of patients with low back pain. Fluid in the joint, bone marrow edema and soft tissue swellings can be identified by MRI. The diagnostic sensitivity of MRI for sacroiliitis is about 54% [29]. The Spondyloarthritis International Society has developed assessment criteria for the diagnosis of sacroiliitis in spondyloarthritis. MRI can identify inflammatory changes of the joint at very early stages [30,31] and can thus help in the management and treatment of complex diseases such as ankylosing spondylitis [31]. MRI can also differentiate between rheumatic and non-rheumatic changes in the sacroiliac joint [32].

Single-photon emission computed tomography and bone scintigraphy can be used for assessment of sacroiliac joint pathology but are not routinely practiced [33]. The current gold standard for diagnosis of sacroiliac joint dysfunction is injection of a local anesthetic solution into the joint guided by fluoroscopy or computed tomography: if the injection relieves pain, the sacroiliac joint can be confirmed as the pain source. The simultaneous analysis of bone computed tomography scans and radiography can help diagnose joint changes and progression of disease with an accuracy up to 95% [34].

Although most patients with an accessory sacroiliac joint do not complain of chronic low back pain, they may have chronic buttock or low back pain, especially with severe arthritis and degenerative changes. Using computed tomography to assess low back pain, accessory sacroiliac joints have been identified as the cause of pain in 4.5% of patients under 40 years [35]. In one case, a patient was diagnosed with an accessory sacroiliac joint and had severe arthritic changes in the right sacroiliac joint [36]. Another case of an accessory sacroiliac joint was misdiagnosed as ankylosing spondylitis or spondyloarthritis, because the patient was under 45 years, had pain prior to the appearance of degenerative changes, and developed arthritic changes due to the accessory sacroiliac joint over a period of 7 years [37]. An accessory sacroiliac joint may therefore be a cause of sacroiliac pain and should be included in differential diagnosis for better management of the disease.

2) Sacroiliitis

In most cases, sacroiliac joint dysfunction is seen as a result of micro-trauma. Acute or repetitive microtrauma may cause low back pain in 10%-30% of patients [2]. The trauma mostly results from physical activities like heavy lifting or prolonged bending, or may be a result of a rear-end motor vehicle collision [38]. The pain can be managed through activity modification, medication, physical therapy, and/or injections. In cases of prolonged sacroiliac joint pain, clinicians should look for other potential etiologies. Sudden rotation and/or axial strain is the most common mechanism underlying acute sacroiliac joint pain [39]. People involved in physical activities requiring repetitive and/or asymmetric body movements are at high risk [40].

An example of an activity that involves asymmetric body movements is rowing. In fact, during rowing, the transverse plane load is applied through the lumbosacral region while the pelvis remains relatively inactive. This disrupts normal equilibrium and results in unbalanced muscle action around the pelvic and sacroiliac region. A study on rowing teams reported a > 50% prevalence of sacroiliac joint dysfunction in rowers tested by the standing flexion test, and an examination of anatomical landmarks [41]. Similarly, other sports involving asymmetric techniques...
such as V-skating can also lead to lumbosacral dysfunction [42].

Low back pain is also rarely reported in children aged 5 (1%) to 15 years (53%) [43]. A strong positive association between adolescent idiopathic scoliosis, abnormal curvature of the spine, and sacroiliac joint dysfunction was observed in athletes up to 17 years of age in a case-control study [44]. Seronegative spondyloarthopathy and ankylosing spondylitis were reported in a young male athlete who did running, jumping, and weightlifting. The case was initially misdiagnosed as sacroiliac joint instability and sacroiliac joint dysfunction; later a stress fracture was diagnosed [45]. In addition to these specific examples, other sporting activities involving biomechanical stress on the spine and pelvis can cause low back pain, sacroiliac joint dysfunction, and related diseases. As the lumbospinal region connects the torso and the lower extremities, it is at high risk of athletic injury since most sports stress this region.

3) Treatment options

Conservative treatment of sacroiliitis involves management of pain with activity modification, physiotherapy, manual manipulation, topical medication such as lidocaine and diclofenac, and oral medication, usually non-steroidal anti-inflammatory drugs [2,46]. Complementary treatment regimens can also be helpful in pain management but cannot be considered treatment options for sacroiliac joint pain [2]. Massage, yoga, and acupuncture are thought to relieve the pain; the effect is not long-lasting but can complement conservative treatment. Treatment goals for spondyloarthritis not only include management of symptoms but also treatment of underlying dysfunction [40].

Osteopathic and other manipulative treatment include manual techniques used to treat or prevent injury or illness. Muscles and joints are moved using stretching, resistance, and applying gentle pressure to periarticular structures. Osteopaths, chiropractors, physical therapists, and athletic trainers use various forms of osteopathic manipulative treatments, depending on their specialties [33]. Up to 95% of patients respond to such treatments and show excellent short-term results. Long-term benefits and recurrence prevention after osteopathic manipulative treatment have not yet been proved [33].

Interventional treatment may include neurostimulation, joint injections, radiofrequency denervation, and joint fusion. Neurostimulation provides pain relief through modulation of the nervous system. Among neurostimulatory therapies, peripheral nerve field stimulation is used for sacroiliac joint pain. Two permanent subcutaneous electrodes are implanted in the upper buttock below the iliac crest. Neurostimulation is used in patients in which pharmacological or physical therapies have failed. The mechanism of action of peripheral nerve field stimulation is unknown, although a number of hypotheses have been put forward: inhibition of the pain pathway through the counter-stimulation of the sensory fibers that innervate the affected region, changes in endorphins and other neurotransmitter release, as well as local blood flow changes [47,48].

Corticosteroids can be injected into the sacroiliac joint to reduce inflammation and pain [49]. However, there is no clear evidence that they are actually effective [50,51]. Furthermore, too many injections may weaken bones and tendons, therefore the administration can be performed only a few times per year [52].

Radio frequency denervation (or neurotomy) consists of an insulated needle electrode with the exposed tip adjacent to the nerve branches that reach the target joints. The radio frequency applied to the electrode heats the adjacent tissues and ablates the nerve that innervates the joint. The effectiveness of this technique has not been clearly established in randomized controlled trials [53].

In severe cases, fusing the two bones together with a metal device may be used to treat sacroiliitis. The implant placement is performed under general anesthesia. The ilium is reached after an incision in the buttock region, and the dissection of the gluteal fascia. After that, the sacrum is reached using a drill through the iliac bone to the sacrum. At the end of this procedure, three implants are placed. The upper implant is placed within the ala of sacrum. The other two implants are located adjacent to the S1 foramen, and between the S1 and S2 foramina, respectively [54]. Since the pain is caused by the movement of the sacroiliac joint, it is reasonable to think that blocking this joint, through the sacroiliac joint fusion, would result in a reduction of pain. The implant placement is performed under general anesthesia. The ilium is reached after an incision in the buttock region and the dissection of the gluteal fascia. After that, the sacrum is reached through the use of a drill that punches the iliac bone to the sacrum. At the end of this procedure, three implants are placed. The upper implant is placed within the ala of sacrum. The other two implants are located adjacent to the S1 foramen, and between the S1 and S2 foramina, respectively [54]. This technique seems to be highly effective at reducing pain [55-57].

3. Molecular biology of sacroiliitis

Sacroiliac arthropathies are known to be highly recurrent within families. First-degree relatives are at high risk of developing ankylosing spondylitis, about 52 times higher
than unrelated individuals [58]. The association of environmental and genetic factors in ankylosing spondylitis was unclear until the early 1970s, when the human leukocyte antigen-B27 (HLA-B27) allele was found to be associated with the disease [59,60].

1) MHC and non-MHC associations

HLA-B27 in major histocompatibility complex (MHC) class I contributes to immune system dysfunction. There is a strong association between the HLA-B27 gene and ankylosing spondylitis, one of the strongest links of a gene with a human disease, although the underlying molecular mechanism is still unclear. Association of HLA-B27 with autoimmune diseases has been widely studied and 130 subtypes of HLA-B27 have now been reported. Since most patients with Crohn’s disease have symptoms of low back pain and sacroilitis, positivity for HLA-B27 in these patients places them at high risk of developing axial inflammation [61]. However, the relation of HLA-B27 with sacroilitis needs more extensive research, since some reports suggest a lack of association, as no antibodies were found in patients with inflammatory low back pain [62] or isolated sacroilitis [61]. Another report demonstrates a weaker association of HLA-B27 in inflammatory bowel disease-associated spondyloarthritis than in idiopathic ankylosing spondylitis [63].

In a case report, Eksioglu et al. [64] postulated that use of isotretinoin might trigger sacroilitis in combination with HLA-B27 positivity, although this was not confirmed in other cases. In another study, Kaşıfoğlu et al. [65] observed that 32.7% of patients with familial Mediterranean fever had symptoms of sacroilitis, 47% of whom were also HLA-B27 positive. This data suggests possible involvement of HLA-B27 in the development of sacroilitis and in the severity of seronegative spondyloarthropathy. Though extensively studied, the contribution of HLA-B27 to the genetic risk of developing spondyloarthritis is minimal. Polymorphisms in genes outside the MHC class I region have also been found to be associated with development of sacroilitis and ankylosing spondylitis. These involve various cytokines, such as interleukin 1 (IL-1) and its receptor IL-1R, IL-23, and tumor necrosis factor α (TNFα) [66].

Although IL-1 could be implicated in sacroilitis, there is no direct evidence of its presence in joint biopsies. Genes encoding IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1RA) contain various polymorphic sites which affect the production of cytokines, and are involved in joint destruction [66]. Linkage studies have shown that the long arm of chromosome 2 has a strong correlation with the development of ankylosing spondylitis. As the IL-1 family of genes is located on 2q13, their alleles could be useful markers for genes potentially involved in the pathogenesis of this disease [67]. The IL-1RA binds IL-1, competitively inhibits IL-1 binding with its own receptor, and prevents signaling through the IL-1 receptor [68]. Studies have shown that disruption of the IL-1 signaling cascade prevents bone damage and joint erosion in animal rheumatoid arthritis models [66,69]. The gene encoding IL-1RA has a variable number of tandem repeats in intron 2. Based on the number of repeats, different alleles have been identified. An allele with two repeat sequences (allele 2 of IL-1R) is known to increase production of IL-1RA in vitro [67]. Studies in human subjects have also shown a high frequency of allele 2 of IL-1RA in ankylosing spondylitis patients compared to healthy controls. Although no difference in the preferred polymorphic allele of the IL-1α and IL-1β genes was observed in this study [70], association of polymorphisms of IL-1α and IL-1β with ankylosing spondylitis susceptibility has been observed in the Han Chinese population [71].

Polymorphism of the IL23R gene and surrounding regulatory region shows a strong association with risk of ankylosing spondylitis [72,73], inflammatory bowel disease [74], and psoriasis [75]. An association between rs11209026 and ankylosing spondylitis was observed by Kadi et al. [76] in the French population. However, this association was limited to spondyloarthritic patients with radiographic sacroilitis. This finding reinforces the evidence that IL-23 is involved in the development and progression of these diseases, and suggests that IL-23 may be the key cytokine controlling many disease manifestations of ankylosing spondylitis and other spondyloarthropathies [76].

Proinflammatory cytokine TNF is involved in inflammatory conditions such as sacroilitis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and Crohn’s disease. Overexpression of TNF may cause sacroilitis, as TNF blockade treatment in patients with ankylosing spondylitis has been demonstrated to bring significant benefits and outcomes [77,78]. Development of bilateral erosive sacroilitis with synovial inflammation, bone erosion, and cartilage destruction have also been observed in transgenic mice overexpressing TNF. These inflammatory changes were inhibited when TNF was blocked using infliximab antibody and signs of sacroilitis were reduced in treated mice compared to the wild-type [79].

Variants in the CARD15 gene have been linked to a higher susceptibility for Crohn’s disease. An association was observed between CARD15 variants and the development of sacroilitis, as an extraintestinal manifestation of Crohn’s disease [80], although this could not be confirmed in subsequent studies [81].
2) Autoantibodies

Autoantibodies have a strong role in most autoimmune diseases; however, little information is available on their possible role in sacroiliitis compared to other rheumatic autoimmune diseases. Several autoantibodies targeting antigens from connective, skeletal, and muscle tissue have been identified in the blood of patients with ankylosing spondylitis [82]. One of the most studied autoantibodies in ankylosing spondylitis is the antibody targeting protein, phosphatase magnesium-dependent 1A (PPM1A), a serine/threonine protein phosphatase that suppresses bone morphogenetic protein and regulates Wnt signaling [83]. Overexpression of PPM1A dephosphorylates the transcription factor involved in skeletal and osteogenic development [84]. Significantly higher levels of anti-PPM1A autoantibodies have been observed in patients with more advanced sacroiliitis. Additionally, a positive correlation between levels of antibodies and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has been found after treatment with anti-TNF agents. Similarly, higher levels of anti-PPM1A autoantibodies have been observed in the serum of transgenic rats predisposed to spondyloarthritis compared to controls. Increased levels of PPM1A in ankylosing spondylitis synovial tissue promoted osteoblast differentiation, whereas down-regulation of PPM1A suppressed it. The data suggests that PPM1A may contribute to the pathogenic bone ankylosis typical of ankylosing spondylitis [85].

Anti-citrullinated cyclic peptide is commonly detected in rheumatoid arthritis patients and individuals with joint inflammation. These antibodies have also been detected in patients with various clinical presentations. For example, anti-citrullinated cyclic peptide was found in a patient initially diagnosed seropositive for rheumatoid arthritis with involvement of the sacroiliac joint. Another patient showed a clinical picture of rheumatoid arthritis after an Escherichia coli-positive urinary tract infection; and two patients had asymmetrical sacroiliitis, without peripheral joint involvement. In all cases, high titres of anti-citrullinated cyclic peptide were found. The report suggests an overlap between rheumatoid arthritis and spondyloarthritis, as well as an association of high titres of anti-citrullinated cyclic peptide with asymmetrical sacroiliitis and reactive arthritis in patients with no peripheral small joint involvement [86].

3) MicroRNAs

In one study, Prajzlerová et al. [87] observed significantly higher expression of miR-29a-3p in patients with progressive spinal disease compared to healthy controls. No correlation between microRNA levels and BASDAI was found in these patients. Other microRNAs selected in this particular study included miR-146a-5p and miR-222-3p. They have an established role in extracellular matrix formation and inflammation. All these microRNAs have been associated with spinal changes and/or disease activity assessed by BASDAI in ankylosing spondylitis patients.

In another study, Huang et al. [88] observed significantly higher expression of miR-29a in peripheral blood mononuclear cells of ankylosing spondylitis patients than rheumatoid arthritis patients and healthy controls, while no significant difference was observed between the rheumatoid arthritis patients and healthy controls. Although this elevated expression was not correlated with the disease activity index of ankylosing spondylitis patients, miR-29a might be a useful diagnostic marker of new bone formation. Similarly, elevated expression of miR-29a, miR-17-5p, miR-27a, and miR-126-3p was observed in peripheral blood mononuclear cells of patients with axial spondyloarthritis. No other clinical features were correlated with these four microRNAs in patients with ankylosing spondylitis. The highest expression was observed for microRNA-29a, which may therefore have potential as a diagnostic marker in axial spondyloarthritis [89].

4) Microbiome

The established relationship between joint inflammation, intestinal inflammation, and co-occurrence of these diseases is a captivating issue. Since sacroiliitis is closely linked with intestinal diseases like inflammatory bowel disease and Crohn’s disease, gut microbiota might play an important role in its development. Ileocolonoscopy studies found involvement of the gut in 25% to 75% of spondyloarthritis patients depending on subtype. Follow-up studies have shown development of Crohn’s disease in about 6% of these patients [90]. The findings have also been confirmed via abdominal scintigraphy with labeled leucocytes, showing signs of intestinal inflammation in 50% of patients [91].

An association between classic enteropathogenic bacteria, i.e., Yersinia, Salmonella, Shigella, and Campylobacter, has been observed with post-infectious spondyloarthritis and rheumatoid arthritis [92,93]. Escherichia coli [94] and Clostridium difficile [95] have also been implicated in rheumatoid arthritis. The anti-inflammatory strain, Faecalibacterium prausnitzii seems depleted in spondyloarthritis patients, suggesting a probable effect on the immune system [96]. Specific bacterial strains have been found to play an important role in the pathogenesis of ankylosing spondylitis. These strains include Klebsiella pneumonia [97] and Bacteroides vulgatus [98]. The effect of host genetics in determining the human microbiome in health and disease
A shared immunological link has been proposed by Baeten et al. [99] in the form of two hypotheses. One is the homing hypothesis based on the aberrant localization of T cells (particularly CD8+ T cells) in synovial fluid after priming in the gut; the other is based on altered trafficking of CD163+ antigen presenting cells. These macrophages activate particular lymphocytes, increasing production of TNF-α and decreasing synthesis of IL-10. Cytokines other than TNF-α may also be involved in the pro-inflammatory cytokine cascade, as a large subset of patients with spondyloarthopathies and inflammatory bowel disease do not respond to anti-TNF-α therapy [99]. It is therefore crucial to understand the exact basis of shared inflammatory pathways, gut microbiota, and joint inflammation.

CONCLUSIONS

Sacroiliitis and spondyloarthopathies are common causes of low back pain in people involved in repetitive asymmetric activities. In assessing patients with pain in the low back, or radiating to the thigh and calf, the clinician must bear in mind the possibility of sacroiliac joint inflammation and accessory sacroiliac joints. Sacroiliitis is usually the first manifestation of more complex spondyloarthopathies like ankylosing spondylitis, inflammatory bowel disease, Crohn’s disease, psoriasis, and rheumatic disease. No single diagnostic technique can detect sacroiliac joint dysfunction with high sensitivity and specificity. Available techniques like computed tomography scans or MRI cannot differentiate symptomatic from asymptomatic patients. This review aims to provide clinicians, physicians, and researchers with concise information on the anatomy, physiology, and genetics of the sacroiliac joint for a better understanding of the etiology of sacroiliitis in the general population. Knowing genetic pre-disposition for sacroiliitis can be useful for diagnosis and for formulating treatment regimens, and may lead to a substantial reduction in disease severity and duration, and to improved patient performance.

CONFLICT OF INTEREST

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Etiopathogenesis of sacroiliitis

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Etiopathogenesis of sacroiliitis

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