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Coxitis in axial spondyloarthritis: the unmeasured, yet functionally most important, radiographic progression

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While spinal involvement in patients with axial spondyloarthritis (axSpA) gets all the attention, extra-spinal joint involvement can pose a major physical and functional burden for these patients. Along with the shoulder, hip joints are considered "root joints" in ankylosing spondylitis (AS).[1] Involvement of these joints has a major social and economic impact, restricting activities of daily life. The hip is the most frequently affected non-spinal joint in AS, and in juvenile spondyloarthritis (SpA), severely affecting mobility and carrying a high risk for major incapacity, particularly in the young patients.[2,3] Hip involvement can occur independently from spine damage[4] and it was shown that hip rather than spine involvement contributed more for a worsening in Bath AS Functional Index in older patients.[5] Despite this, large randomized controlled trials have evaluated spinal and sacroiliac joint damage as a prognostic surrogate for incapacitation.[6] To put it simply, what is the clinical consequence and/or relevance of fused sacroiliac joints? The answer: None.

A recent worldwide survey reported that hip involvement across the spectrum of SpA varied from 27% in those with psoriatic arthritis up to 53% in juvenile SpA, being more common among Asian patients.[7] These very recent data suggest that the prevalence of hip involvement at least in SpA may not have changed over time, since previous cohorts have reported a 24% to 36% variation in prevalence of hip involvement in AS.[3] However, there are no prospectively collected data evaluating severity of hip damage in AS, let alone in the whole SpA spectrum of diseases. Total hip replacement (THR) can be a "game changer" procedure in the quality of life in young patients with SpA and severe hip involvement.[8-12] However, it carries a major risk for joint infection as well as a possible need for surgical revision in later years. Some patients may either not be willing to undergo surgery, or circumstances may make the surgical procedure not possible. Thus, using the number of THR performed is far from an ideal surrogate parameter to document failure of medical therapy to halt progression of hip damage in SpA. In reality, the number of THR procedures in AS patients have increased from 1999 to 2013, particularly in the older patients. This should not be construed as suggesting a worsening prognosis, or increased occurrence of end-stage damage to the hip, but in fact improvements in surgical techniques, reductions in the duration of the operating time, and post-surgical complications, as well as decrease in the need for revision surgery, might have led to this increased number of THR.[8,9,13] This paradox can be illustrated by an earlier report showing a trend towards lower incidence of THR as well as an increase in the age of AS patients being subjected to THR,[11] whereas a more recent study questioned those data and reported an increased number of THR procedures in AS patients with no apparent risk reduction following the introduction of tumor necrosis factor inhibitors (TNFi) to treat AS.[14]

The pathophysiology of joint damage in AS characteristically includes inappropriate osteogenesis. Those *de-novo* lesions of bone formation present as syndesmophytes and enthesophytes in the spine and extra-spinal joints imaging, respectively.[15] On the contrary, inflammation of the hip in axSpA presents as a destructive erosive process, with areas of bone cysts and collapse of the femoral head with irreversible damage of the femoro-acetabular joint. Those changes mimic the synovitis encountered in other chronic inflammatory arthropathies, for example, rheumatoid arthritis, with prominent cell influx, effusion, and joint erosion.[3,16] Theoretically, this similarity could suggest common pathophysiologic mechanisms, thereby opening the possibility of different therapeutic approaches when managing spinal *vs.* extra-spinal involvement in SpA. It is

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also worth noting that the hip joint is characterized by a relatively low blood supply, with limited anastomosis furnishing the femoral head. Indeed, a rapid development of avascular necrosis of the femoral head occurs after a compromised blood supply. Thus, groin pain is a signal for clinical alert in patients when avascular necrosis of the hip is suspected, prompting immediate intervention.[17] It might well be that a similar urgency applies when hip involvement in SpA is suspected.

As mentioned above, early hip damage represents a bad prognostic sign in SpA, which was shown to be independent from radiographic progression of spine damage in AS.[5] Similar to what happens in avascular necrosis of the hip due to other causes, relying on symptoms such as pain in the groin may well be too late if we intend to prevent further joint damage. THR means "painless walking" for a patient with end-stage hip damage in SpA.[9] Moreover, THR accelerates return to work, with obvious positive impacts both at the individual and societal level[18] with acceptable costs.[9,11] However, avoiding or postponing THR in SpA would be a clinical objective. In clinical practice, hip involvement in SpA is based on symptoms and physical examination followed by radiography.[2,7] Although a BASRI score for the hip has been sometimes used, it lacks correlation with clinical findings besides displaying a low sensitivity to change.[14,19]

Non-steroidal anti-inflammatory drugs provide symptomatic benefit in early stages of axSpA, but the conventional synthetic disease modifying antirheumatic drugs are neither of benefit nor have been shown to halt disease progression.[8] Evaluation of the hips of patients with AS using power Doppler ultrasonography showed inflammatory and structural changes, which were reduced following treatment with a TNFi.[20] Also, a very recent report used magnetic resonance imaging (MRI) to demonstrate reduction of inflammatory signs in the hip of AS patients treated with a TNFi.[21] Considering that biologic disease modifying antirheumatic drugs (bDMARDs) such as TNFi and interleukin-17 inhibitors provide clinically significant pain relief, and TNFi possibly reduce the rate of radiographic progression in the spine in retrospective observational studies,[22] it would be interesting to see if they could also halt hip damage in SpA. While we are not aware of prospectively collected data demonstrating a hip sparing effect for TNFi or other bDMARD in SpA, we recently published a case series illustrating that treatment with TNFi prevents clinical and radiological progression of hip damage in AS. Withdrawal of the medication in one of our four patients with a seriously compromised hip led to rapid destruction of the joint, followed by arthroplasty. In that report, we described findings from literature review showing other case series suggesting that TNFi might well halt hip damage in SpA.[1] Despite these data, there are no explicit recommendations in the current guidelines to start bDMARDs early in a patient with AS and groin pain.[8,7]

Early referral is considered a major unmet need in diagnosing SpA. It seems undisputable that we are still struggling to improve recognition of inflammatory chronic low back pain in the primary care setting as a strategy to shorten the time to diagnosis.[23] Given the burden that destruction of the hip may represent particularly to younger patients with SpA, early recognition is also of utmost importance if we are to prevent joint replacement. It is not uncommon to see an MRI of the sacroiliac joints being performed without even having a prior plain X-ray of such joints, despite remaining the gold standard exam for defining radiographic axSpA. However, recommendations of when and which imaging procedure should be done for early recognition of hip damage in SpA are yet to be published. Conducting prospective trials, even short-term, could provide answers for interventions attempting to halt hip damage in SpA. Given that a long-term placebo arm could be considered unethical, establishing a randomized protocol with a very early escape option allowing a change to the interventional arm, could provide relevant data, probably with the help of hip imaging. Alternatively, are we already sufficiently informed to advise the start of a bDMARD, possibly a TNFi that has shown some positive data, in treatment guidelines to prevent hip damage based on plain radiography? At this time, we believe that persistent pain in the groin of a patient with a diagnosis of SpA immediately justifies evaluation by a rheumatologist to order imaging studies aiming to detect signs of hip compromise. Provided imaging data match the clinical picture of hip damage, prompt institution of bDMARD deserves consideration.

Conflicts of interest

Francisco Airton Castro Rocha: Consulting, Advisory Boards: Aché, Abbott, BMS, Grunenthal, Janssen, Novartis, Pfizer, Zodiac. Atul Deodhar: Consulting, Advisory Boards: AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Galapagos, Glaxo Smith & Kline, Janssen, Novartis, Pfizer, UCB.

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