Editorial

Potential insights into the role of biomechanical stress in axial spondyloarthritis from idiopathic hypoparathyroidism, a rare disease with intriguing skeletal manifestations

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Despite great progress in the treatment of patients with axial spondyloarthritis following the introduction of targeted therapies that block pro-inflammatory cytokines tumour necrosis factor (TNF) and interleukin-17, onset and initiating mechanisms of disease remain ill understood. Preclinical studies have provided support for biomechanical stress as trigger for disease (1). Whereas inflammation-induced loss of bone mass and stability in the spine and the sacroiliac joint (SIJ) have been suggested as factors driving the progressive ankylosis of the SIJ and the spine in the subpopulations of patients suffering from the ankylosing spondylitis (AS) subtype. In this issue of the journal, Masi and colleagues describe a series of intriguing novel observations on the association between idiopathic hypoparathyroidism (iHPoPT) with an axial spondyloarthritis (SpA)-like phenotype (iHPoPT/SpA) (2). As described in a comprehensive review of 14 cases from the literature, patients with iHPoPT/SpA (11 male, 3 female) all presented in middle age (range: 29–62 years) with insidious onset of a combination of clinical (axial skeleton pain, stiffness, limitation of motion, and AS-like posture) and radiographic (syndesmophytes and enthesophytes) features of SpA. When compared to a Spanish cohort of 842 patients with AS, iHPoPT/SpA had greater involvement of neck and hip symptoms and were significantly older at age of disease onset and diagnosis (3). Notably, in iHPoPT/SpA, radiographic evidence of sacroiliitis and HLA-B27 positive status were found in one and two cases, respectively. The authors conclude that iHPoPT/SpA is a clinical phenotype with SpA-like radiographic signs of disease and explore potential differences and commonalities between iHPoPT/SpA and AS in terms of immunological and biomechanical pathophysiologic contributions (2).

iHPoPT is a rare genetic disease characterised by low parathyroid hormone levels and low serum calcium leading to predominant clinical manifestations of neuromuscular irritability (4). Aside from muscle cramps and tetany caused by neuromuscular hyperactivity, ectopic calcifications (*i.e.* nephrocalcinosis, corneal calcifications) also occur in hypoparathyroid disorders; however, these calcium deposition features are considered more related to treatment with calcium and vitamin D supplementation and not hypocalcaemia itself. Thus, the axial symptoms and enthesophyte/syndesmophyte formation seen in the iHPoPT/SpA cases – where hypoparathyroidism was diagnosed and managed *after* SpA symptom onset – are suggested by Masi *et al*. to be best interpreted as being caused by chronic and excessive neuromuscular input as opposed to altered calcium metabolism. Masi *et al* effectively suggest that the SpA-like phenotype evident in iHPoPT supports a hypothesis that excessive and sustained muscle contraction contributes to SpA pathogenesis in those with genetic and immune predisposition (2). Although these observations are far from being conclusive evidence, they are nonetheless an important initial contribution to understanding thus far elusive biomechanical contributors to SpA based on patient observations.

Other observational evidence in both SpA and conditions with similar pathoanatomic localisation support a role for mechanical stress in SpA pathophysiology. For example, osteitis condensans

ilii (OCI) is a non-inflammatory condition characterised by sclerosis (with or without pain symptoms) of the ilial side of bilateral SIJ. Given that OCI classically occurs in the peripartum period, SIJ changes are attributed to mechanical strain and relaxation of the pelvis to support child birth (5). Further, SIJ abnormalities mimicking SpA on MRI (*i.e.* bone marrow oedema) are commonly found in both postpartum women (6) and athletic populations (7). Since the SIJ are critical for proper transfer of loads between the lower extremity and spine (8) and both childbirth and athletics impart exaggerated stress through the SIJ, there is a logical biomechanical connection between the osseous abnormalities seen in these benign conditions with sacroiliitis and bone formation in SpA.

The pathophysiology of SpA is incompletely understood and involves multiple interconnecting factors, including genetic risk and altered innate immune, adaptive immune, and tissue repair pathways (9). Since it remains uncertain whether current standard-of-care therapies (*i.e.* TNF inhibitors) can fully prevent spinal damage and bone formation in AS (10), it is essential to better understand all of the contributors to SpA pathogenesis, including biomechanical factors. Even though chronic mechanical stress through the SIJ and entheses is commonly cited as a potential trigger for early disease (9), the exact nature of biomechanical inciters remains unknown. Of note, the hypothesised mechanisms contributing to onset of disease (*i.e.* local microdamage) differ from insights into the new bone formation process where a role for systemic bone loss and instability triggered by inflammation, was recently suggested (11).

Studies from animal models and humans indeed highlight the link between both excessive extrinsic (*e.g.* loading, microinjury, and trauma) and intrinsic (*e.g.* inherent properties of muscle-tendon-enthesis unit) biomechanical factors to inflammatory arthritis and enthesitis in SpA. Regarding animal models, study of a TNF-driven model of SpA showed that hindlimb unloading prevented inflammatory disease onset, whereas overloading from voluntary running in both collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA) models contributed to arthritis progression (12). Additionally, in a survey of over 1000 patients with AS, nearly half cited injury or trauma as an inciting factor in their disease onset (13). Giving evidence to possible intrinsic biomechanical factors, a cohort of 24 AS patients was found to have greater lumbar paraspinal muscle resting stiffness as measured by myotonometry compared to age- and sex-matched healthy controls (14). The primary question from this study is whether differences in muscle biomechanical properties contributed to or were caused by SpA pathogenesis (*i.e.* the chicken *versus* the egg phenomenon). As an important step forward, observations from the Masi *et al.* study give more support that intrinsic myotendinous alterations (*i.e.* chronic neuromuscular overactivity) may contribute to SpA symptoms and enthesopathy (2). Ultimately, clarification of the potential biomechanical contributors will be critical for proper patient and family member counseling regarding SpA treatment and prevention.

Despite the question of mechanical loading from physical activities contributing to disease onset and perpetuation in SpA, there is also significant evidence supporting the beneficial effects of exercise and physical therapy on SpA disease activity, pain, and function (15). These contrasting findings regarding exercise in SpA suggest that perhaps there is an optimal amount of physical activity along the spectrum between detrimental and beneficial mechanical loading (11). However, there remain several unanswered questions regarding the specific mode, dose, and intensity of exercise to prescribe for SpA. For instance, for persons with exaggerated inflammatory and repair responses to physical loading, does avoidance of high-intensity activities (*i.e.* those that impart high loading through SIJ and entheses) help in preventing SpA progression? Conversely, for persons with or at-risk for SpA who have intrinsic muscular hyperactivity or hypertonicity, are mobility, stretching, and muscle relaxation activities (*e.g.* yoga or massage therapy) most helpful? Further, what is the effect of pharmacotherapy combined with exercise (*e.g,* TNF inhibitors with resistance and aerobic training) on preventing damage and bone formation in SpA? Finally, do current approaches that include muscle strengthening, in particular for the core, increase muscular contributions to stability of the spine and thereby reduce the need for a stabilising endogenous ankylosing response? To answer these challenging questions, further well-designed studies are needed to: 1) better understand the specific biomechanical mechanisms and molecular signalling in SpA; 2) develop clinical tools to assess SpA biomechanical alterations; and 3) create specific physical and pharmacologic interventions targeting biomechanical pathways. Future keen observations and clinical reasoning – such as those from Masi *et al* and others in this field – will ultimately advance knowledge of the biomechanical factors contributing to SpA to the benefit of all patients with inflammatory arthritis.

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