Osteoporosis: a paradox in Ankylosing Spondylitis

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Ankylosing spondylitis (AS) is a remodelling arthritis characterised by chronic inflammation and new bone formation. Ankylosis of the axial skeleton and sacroiliac joints leads to an impairment of spinal mobility and an increased risk of spinal fracture. While inflammation originates in the entheses, the anatomical zone in which tendons, ligaments and capsules insert on to the underlying bone, inflammation also exists within the bone marrow (osteitis). Histological analysis of bone from AS patients shows mononuclear cell aggregates and increased osteoclast activity in affected joints or vertebrae [1]. Some hypothesise that these processes are associated with new bone formation in AS, while other observations suggest that bone apposition in AS is not induced by direct exposure to inflammatory infiltrates [2]. The latter concept is supported by the simple notion that inflammation is considered detrimental to bone formation, a fact which is further supported by the occurrence of secondary osteoporosis in AS.

Detecting osteoporosis in AS

Although it seems somewhat paradoxical to have bone loss associated with a disease characterised by excessive bone formation, the former is a consistent feature of inflammatory disease. Rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease are all associated with secondary osteoporosis, and AS is no different. Even in the early stages of disease, osteoporosis is a common complication of AS [3]. However, there are large discrepancies in the reported incidence. Incidence varies from 18.7% to 62% [4, 5], which is most likely due to the difficulties that are encountered when measuring bone mineral density (BMD) in AS patients. Measurements can vary substantially depending upon the chosen anatomical site, the particular technique applied and the degree of ossification. There are limits to the accuracy of spinal DEXA measurements, which have found to be unreliable in the presence of syndesmophytes and hyperossification [6]. Consequently, measurements at alternative sites, such as the femoral neck, are required in order to assess BMD in patients with advanced disease. Not only is femoral neck BMD considered to be a more reliable measure, but it also correlates well with vertebral fracture risk and the degree of inflammation [7]. To date, the

majority of studies report decreases in BMD at the femoral neck in AS in both early and late stage disease, with bone loss more prevalent in AS patients with syndesmophytes [4, 8].

Aetiology of osteoporosis

The specific aetiology of osteoporosis in AS is complex and potentially involves several factors. One early hypothesis suggested that immobility associated with pain, stiffness and eventual ankylosis was the likely cause of bone loss in AS [9]. The concept was constructed around the theory that the extraspinal bone in advanced disease dispersed gravitational, motional and compressive stresses in the vertebral trabeculae, resulting in decreased trabecular density. However, as osteoporosis is also present in patients with early disease, devoid of any functional impairment, it is likely that systemic factors also contribute to bone loss in AS [10]

In fact, several studies have shown that in AS there are significant correlations between markers of bone turnover, proinflammatory cytokines and acute phase reactants [7, 11, 12]. This suggests that these systemic inflammatory mediators play a role in modulating bone turnover in AS. More specifically, TNF α , IL1 and IL6 levels have been shown to correlate with several bone turnover markers (PYD, DPYD, osteocalcin) as well as standard measures of inflammation (ESR, CRP) in other rheumatic diseases [13, 14]. Furthermore, serum concentrations of both IL6 and TNF α are increased in patients with AS compared to subjects with noninflammatory back pain [15]. IL17 is yet another cytokine that is increased in AS patients that may be implicated in the development of secondary osteoporosis [16]. IL17 not only stimulates TNF α production, but has also been shown to mediate bone erosion via alterations in the RANKL/OPG balance [17, 18]. As OPG functions as a soluble receptor for RANKL, serving to neutralise RANKL and osteoclast formation, it is not surprising that low serum levels of OPG have been associated with osteopenia in AS [11]. Nonetheless, consistent associations with disease progression have yet to be demonstrated [19, 20].

Cell and molecular processes

The role of the osteoclast in AS is less defined than in rheumatoid and osteoarthritis. In AS, there is an initial bone-resorptive phase that is thought to be the result of local damage caused by mechanical stress and inflammatory triggers. However, new tissue formation, in particular bone formation in the presence of chronic inflammation, is an unusual and contradictory event. AS appears to be quite unique from this perspective and debate continues as to whether bone formation is a secondary process, which can be defined as abnormal repair response after damage, or an intrinsic and primary feature of the disease. More recently, a study by Appel *et al* [21], reported an increase in the number of osteoclasts in zygapophyseal joints of AS patients, compared to non-diseased controls, implying that there is increased remodeling of the trabecular bone in AS, which may also play a role in general bone loss. Conversely, Lories *et al* [22] has previously demonstrated that the bisphosphonate zoledronic acid, a known osteoclast inhibitor, and anti-TNF strategies fail to inhibit ankylosis originating from the entheses in a mouse model of AS, underscoring the notion that unlike rheumatoid arthritis, the osteoclast is not the driving force of AS. However, given the many circumstantial, but well founded links between inflammatory mediators, osteoclast activation and bone loss in AS, more work is required in order to truly define how osteoclasts are behaving both locally and systemically in AS and the role they play in secondary osteoporosis.

Factors beyond inflammation

There are several other factors that may also influence the development of osteoporosis in AS. For example, it is well known that hormones play a role in osteoporosis and positive correlations between BMD and sex steroids have been reported in AS [11]. Additionally, genetic variations in the vitamin D gene, associated with BMD differences have been correlated with both bone metabolism and inflammation in AS [23]. It has also been suggested that vitamin D and calcium metabolism may be disrupted in AS due to the presence of subclinical bowel disease. Bowel lesions can be quite common in AS [24] and this potential disease complication may also contribute to underlying inflammation and subsequent bone loss.

Defining the balance of bone formation and resorption in both AS and osteoporosis has become more complicated by the advent of new factors in bone biology, such as members of the WNT family. The WNT pathway plays a key role in the regulation of bone development whereby WNT proteins induce bone formation and block bone resorption via the induction of OPG. It is therefore not surprising that the WNT inhibitors DKK1 and sclerostin are both potential targets for osteoporosis therapy. These WNT inhibitors have also become the focus of several studies concerning various arthritides. Most notably, the inhibition of DKK1 in human-TNF transgenic mice has been shown to shift the arthritic features of bone erosion and destruction (rheumatoid arthritis-like) towards new cortical bone formation (AS-like) [25]. Given the dramatic effects of DKK1 on bone remodelling, a greater understanding of WNT signalling may be required when considering WNT inhibition as a strategy to combat ankylosis in the presence of osteoporosis. While such a treatment may be effective in inhibiting pathological bone formation, it may also induce generalised bone loss and further the development of osteoporosis in AS. It has been suggested that perhaps the ideal treatment strategy for AS would be to block periosteal bone formation specifically without having an impact on systemic bone mass [2], however, such approaches are yet to be developed.

Currently, there is no general consensus for treating osteoporosis in AS and inhibition of TNF α is considered the most effective approach for reducing symptoms of inflammation in AS patients. There is evidence that anti-TNF therapy may be beneficial for BMD [26] and although few studies have investigated the effect of anti-TNF on BMD in AS directly, several studies in rheumatoid arthritis reporting modest gains in BMD following treatment. Additionally, anti-TNF α therapy had a positive effect on bone turnover markers, with modest increases in bone formation and a decline in bone resorption. Bisphosphonates are widely used to treat osteoporosis and have been considered as an alternative to help improve BMD in AS. Some studies have demonstrated that pamidronate is also effective in reducing disease activity in AS [27].

In conclusion, the concomitant occurrence of local cortical bone growth with systemic bone loss represents an extraordinary paradox in AS. This is a challenge for the development of new therapies that unlike current anti-cytokine strategies also have an effect on ankylosis. The combination of ankylosis and osteoporosis is also likely to increase the risk for spinal fracture as the biomechanical adaptation range of the spine upon loading or trauma is very limited.

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