



CYTOKINE-MEDIATED BONE LOSS IN ANKYLOSING SPONDYLITIS: MECHANISMS AND THERAPEUTIC TARGETS

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ABSTRACT

Ankylosing spondylitis (AS) which is currently categorized under the spectrum of axial spondyloarthritis, is a chronic inflammatory rheumatologic condition that mainly involves the axial skeleton as well as the sacroiliac joints. The disorder is marked by an interplay of genetic predisposition, immunological abnormalities, cytokine signaling, aberrant bone remodeling, and the environment. One of the most significant and paradoxical aspects of AS is the simultaneous occurrence of inflammation-induced bone loss and pathological new bone formation. AS patients may suffer from osteoporosis and vertebral weakness even in the presence of extensive spinal calcification as well as formation of syndesmophytes. The key role in this imbalance belongs to cytokines because of their involvement in the regulation of osteoclasts, osteoblasts, osteocytes, and inflammatory reactions. Tumor necrosis factor-alpha (TNF- α), interleukin-17 (IL-17), interleukin-23 (IL-23), interleukin-6 (IL-6), receptor activator of nuclear factor kappa-B ligand (RANKL), and many other inflammatory agents affect the molecular mechanisms underlying altered bone turnover. The interplay between immune cells and bone forming and bone resorbing cells generates a pathological milieu wherein inflammation, bone resorption, and structural changes coexist at once. This paper will examine the ways cytokines participate in the process of bone loss in AS patients and explore possible treatment options. Special attention will be paid to the axis of TNF- α /RANKL/osteoclasts, IL-17/IL-23, osteoblast and osteocyte regulation, Wnt signaling, sclerostin, Dickkopf-1, and the influence of biological therapy on bone remodeling. Recent studies have shown that inflammatory burden may be effectively decreased via TNF inhibitors and IL-17 inhibitors, thus helping to alleviate the disease symptoms; however, preventing osteoporosis and pathological bone formation remain distinct goals. It may be assumed that better understanding of bone remodeling mediated by cytokines will assist in the development of treatment modalities that would be able to address the issues of inflammation and bone loss at once.

Keywords: *Ankylosing spondylitis, axial spondyloarthritis, cytokines, bone loss, osteoporosis, TNF- α , IL-17, IL-23, RANKL, osteoclasts, osteoblasts, sclerostin, therapeutic targets.*

INTRODUCTION

The hallmark of ankylosing spondylitis is an inflammatory process mainly involving the sacroiliac joints and vertebrae, but the disease might also affect peripheral joints, entheses, eyes, skin, and gastrointestinal organs. AS is one of several variants of axial spondyloarthritis and is highly associated with the presence of certain genes; especially, HLA-B27 plays a crucial role. Yet, the existence of HLA-B27 is not enough to trigger the disease; pathogenesis of ankylosing spondylitis is rather complicated, and it includes genetic, immunological, microbial, and environmental factors. The inflammatory process causes pain,

stiffness, limited motion, and bone changes. Gradually, syndesmophytes and ankylosis occur, leading to spinal stiffness and specific changes in the architecture of bones. In addition, low bone mineral density and a high risk of vertebral fractures are observed among patients suffering from AS, making it a rather unique bone remodeling disorder.

The connection between inflammation and bone metabolism in AS is complicated. In many cases of inflammation, increased inflammatory activity leads to the development of osteoclasts and bone resorption, resulting in the development of osteoporosis. However, in AS, increased inflammation can be associated with overproduction of bone tissue in the affected areas. That is why a patient can have both bone loss in the entire body or within the trabecular bones, and the development of pathological bone tissue in the area around the spine. The paradox described above results from the fact that bone remodeling is a multistage procedure. It includes bone formation, bone resorption, osteocytes' work, mechanical load, and immune system functioning. Cytokines play a role of mediators for these processes.

Bone tissue is a metabolically active tissue constantly being remodelled. Osteoclasts resorb bone and osteoblasts form new bone. Osteocytes are the most numerous cells in mature bone tissue, and they control both resorption and formation of new bone, sensing mechanical and metabolic stimuli and producing proteins, like sclerostin and RANKL. The activity of osteoclasts and osteoblasts is usually precisely balanced in physiological conditions. Inflammation leads to imbalance. Cytokines from immune cells increase the resorption of bone, change osteoblast differentiation, and alter the functioning of osteocytes. All these alterations happen simultaneously with tissue repair mechanisms and enthesial ossification in AS. So, knowledge about the effects of cytokines on bone is important for treating the disease. Conventional anti-inflammatory therapy can relieve the symptoms and inflammatory activity but has varying results in terms of prevention of osteoporosis and structural progression of spine in patients with ankylosing spondylitis. The use of biological therapy targeting TNF- α and IL-17 is a breakthrough in treatment of the active axial disease but does not always produce the same results regarding bone density and radiological progression as concerning inflammatory activity. In this way, the management of the inflammatory response may not be sufficient for correction of the abnormal bone remodelling process. The purpose of the current work is to study the pathways of cytokine contribution to bone loss in AS and assess the main drug targets influencing these pathways. The special emphasis will be laid on such aspects as the TNF- α /RANKL pathway, IL-17 and IL-23 signaling, IL-6, osteoclastogenesis, osteoblast activation, osteocyte-mediated factors, and the Wnt pathway. The role of existing biological treatments and future approaches involving concurrent management of inflammation, osteoporosis and pathological bone formation is also considered.

Pathophysiology of Bone Loss in Ankylosing Spondylitis

BMD reduction in AS is a multifactorial process due to interaction between inflammation, mechanical loading, reduced physical activity, endocrine and metabolic factors, drug treatment, and AS changes affecting bone remodelling. Long-standing AS patients might show decreased BMD at hip joints and peripheral skeleton, while conventional measurements of spinal BMD may be erroneous since syndesmophytes, ligamentous calcification, and other changes in bone architecture cause an increase in apparent BMD of the spine. It means that the presence of bone formation at radiography in spine may

be false in case of AS and does not reflect normal bone quality. Inflammation is the major factor responsible for bone loss. Cytokines produced by activated immune cells affect osteoclasts proliferation and functioning. The crucial role belongs to TNF- α since it enhances inflammatory response and induces osteoclastogenesis directly and indirectly. The TNF- α increases the expression of RANKL and might induce the sensitization of precursors to this cytokine. RANKL binds with its receptor present in osteoclasts precursors and activates intracellular signalling pathway necessary for osteoclast differentiation and maturation. The higher activity of RANKL leads to enhanced bone resorption.

Inflammation also impacts the functioning of osteoblasts. Inflammatory cytokines may inhibit the normal process of osteoblast differentiation under certain conditions but at the same time promote osteogenic processes in certain anatomical sites, for example, entheses. It all depends on the local cellular environment and the activated signalling pathways. So inflammation can stimulate bone destruction in one region and new bone formation in another. It is what makes the reaction unique for spondyloarthritis. There are other cells involved in bone homeostasis maintenance; these are osteocytes that respond to mechanical stimulation and regulate the process of bone formation using certain molecules like sclerostin and Dickkopf-1 (DKK-1). The Wnt/ β -catenin pathway stimulates osteoblast differentiation and bone formation; at the same time, sclerostin and DKK-1 suppress the process of Wnt-signalling. The changes in this pathway might be responsible for the abnormal bone loss/bone formation ratio in AS patients. The lack of mobility also plays a role in bone mineral density reduction. The presence of pain and stiffness in the spine may prevent patients from engaging in physical activity. Physical inactivity is known to inhibit osteoblastic activity, resulting in bone resorption. Thus, there is a strong possibility of an inflammatory response being exacerbated by a mechanical response. Hence, the treatment of AS should include both aspects.

Role of TNF- α in Cytokine-Mediated Bone Loss

One of the best investigated cytokines in AS is TNF- α . It is secreted by activated macrophages, T lymphocytes and other immune/stromal cells and participates in the development and perpetuation of chronic inflammation. TNF- α activates signaling pathways like NF- κ B and MAPK, which lead to secretion of other pro-inflammatory mediators and adhesion molecules. The connection between TNF- α and bone resorption is especially important. TNF- α may induce osteoclastogenesis via the effect on the RANKL pathway. RANKL is synthesized by osteoblastic/osteocyte lineage cells and activated T cells. Binding of RANKL to its receptor RANK located on osteoclast precursors activates NF- κ B and NFAT signaling pathways and leads to osteoclast differentiation. Osteoprotegerin acts as a decoy receptor for RANKL and opposes this process. Thus, the ratio of RANKL and osteoprotegerin is the key point in regulation of osteoclastogenesis.

Continuous action of TNF- α could disrupt this balance towards the development of osteoclasts. Activity of osteoclasts is responsible for degradation of trabecular bone tissue and decrease of its mechanical strength. Moreover, TNF- α could increase the lifespan and activity of osteoclasts thus increasing the rate of bone resorption. Such biological pathway gives an opportunity to understand why there is such correlation between increased inflammation and osteoporosis in AS patients. The importance of treatment with TNF- α is shown by the efficacy of TNF inhibitors in treating AS. The use of drugs like infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab has been proven to result in

betterment of disease activity as well as reduction of inflammatory symptoms. In some instances, there have been reports of stabilization as well as improvement in bone mineral density while under anti-TNF therapy. The above might be attributed to the direct effect of TNF inhibition as well as indirectly due to increased physical activity and decreased systemic inflammation. However, anti-TNF therapy does not completely stop the progression of the structure in all patients. Bone formation continues despite a significant reduction in the inflammation. The above scenario depicts that there exists a relation between inflammation and pathological ossification but they are partly independent of each other.

IL-17 and IL-23 Pathways in Bone Metabolism

IL-23/IL-17 pathway plays a key role in the development of pathologic process of spondyloarthritis. IL-23 induces maintenance and stimulation of particular immune cells that have ability to produce IL-17, while IL-17 acts upon target cells and participates in the inflammatory process of enthesitis and axial skeleton. Even though the function of IL-23 may differ in various experimental systems and human disease, the IL-17 pathway has become an important therapeutic target for treatment. IL-17A is mainly secreted by Th17 cells, although other immune cells like $\gamma\delta$ T cells and innate lymphoid cells can also participate in the production of IL-17. IL-17 induces inflammatory cytokines from fibroblasts, endothelial cells, macrophages and other cells. IL-17 can induce chemokines that can recruit neutrophils and cause local inflammation. As for the bone, IL-17 can affect both osteoclasts and osteoblasts' pathways.

It has been found that the effect of IL-17 on bone is dual and complex. Under some inflammatory conditions, IL-17 has been reported to stimulate osteoclastogenesis by upregulating the levels of RANKL and working together with TNF- α and other cytokines. IL-17 is also involved in the pathological bone formation in the enthesitis through effects on stromal cells and osteogenesis signaling. Thus, IL-17 has been observed to cause destruction and proliferation in bones in a site-specific manner. Both secukinumab and ixekizumab are anti-IL-17A agents that have proven highly effective in axial disease. These agents act by reducing the pro-inflammatory properties of IL-17A, hence providing therapeutic benefits in terms of pain, stiffness, functionality, and disease activity. Further investigations are ongoing regarding their impact on bone remodelling. Similarly, the role of the IL-23 pathway is crucial in biology; however, targeting this pathway therapeutically has proved more complicated than expected in axial diseases. Inhibitors of the IL-23 pathway have exhibited high efficacy in peripheral spondyloarthritis and psoriasis, although this has not been the case in axial AS.

Osteoclastogenesis and the RANKL Pathway

Bone-resorbing osteoclasts are unique multinucleated cells. They arise from lineage precursors such as monocytes/macrophages, which necessitate multiple signals for their differentiation. RANKL is the main osteoclastogenic cytokine; its binding to RANK initiates NF- κ B and nuclear factor of activated T cells signaling. In AS, inflammatory cytokines can increase RANKL levels and the RANKL/osteoprotegerin ratio. TNF- α and IL-17 have the potential to create a pro-osteoclastic environment. In addition, activated T lymphocytes may be involved in the generation of RANKL. Therefore, inflammation may cause an increase in bone resorption despite bone formation in AS.

The RANKL pathway appears to be a promising therapeutic target since the blockade of RANKL can effectively inhibit osteoclast activity. Denosumab, a monoclonal antibody directed against RANKL, is used in the treatment of osteoporosis and various other conditions characterized by bone resorption. It is, however, not a drug comparable to TNF or IL-17 blockers in AS. The use of denosumab in patients with osteoporosis helps improve their bone mineral density and prevent fractures. Nonetheless, this treatment cannot be regarded as a disease-modifying treatment for inflammation of the spine in AS. This difference demonstrates the need to distinguish osteoporosis treatment from treatment of inflammatory diseases. A patient with AS and osteoporosis might need treatment aimed both at inflammation and osteoporosis. Inflammation suppression alone would not help strengthen bones, especially when bone mineral density is already low or there are history of fractures.

Osteoblasts, Osteocytes, and Pathological New Bone Formation

The osteoblasts have the responsibility of creating new bone and form an important part of the pathological process of AS. In the areas where there is enthesitis of the chronic type, inflammatory as well as mechanical factors may lead to the activation of the stromal cells as well as osteoblast-lineage cells, and new bone will be created. This may end up causing syndesmophyte formation and ultimately spinal ankylosis. There is increased recognition of the osteocytes as important regulators of bone formation and resorption balance. They lie in the bone mineralized matrix and interact with osteoblasts and osteoclasts using signalling molecules. Sclerostin which is mainly produced by osteocytes inhibits the Wnt canonical pathway and hence osteoblast function.

The Wnt pathway plays a key role in osteoblast differentiation and bone formation. It causes Wnt proteins to bind to the receptors Frizzled and LRP5/6, thus stabilizing β -catenin and activating transcription of osteogenesis-related genes. Therefore, the inhibition of Wnt proteins can facilitate new bone formation. Research done in spondyloarthritis has indicated that changes in DKK-1 and sclerostin pathways may lead to the development of pathological bone formation. Lower levels of inhibitory signals would allow higher osteoblast activity at the entheses. Meanwhile, inflammation in other locations could promote bone resorption by osteoclasts. This combined mechanism provides a scientific basis for the simultaneous formation of both osteoporosis and syndesmophytes. Thus, the Wnt pathway is a promising yet difficult therapeutic target. Any therapy to inhibit abnormal bone formation while leaving regular bone formation unaffected would need to selectively modulate the signaling pathways locally. While treatment aimed at bone formation would likely exacerbate abnormal spine ossification, treatments to inhibit osteoblast activity might weaken bones.

Role of Other Cytokines and Inflammatory Mediators

Although TNF- α and IL-17 are central cytokines involved in AS, there are several other mediators responsible for bone metabolism. IL-6 is an inflammatory mediator with multi-faceted functions such as inflammation, osteoclastogenesis, acute phase signaling and systemic manifestations of chronic inflammation. Although it can induce osteoclast differentiation indirectly, it does not achieve the desired therapeutic efficacy like TNF or IL-17 inhibition. This shows that the biological significance of a cytokine does not imply its effectiveness when targeted in a clinical setting.

Interferons, granulocyte-macrophage colony stimulating factor, transforming growth factor beta and many other inflammatory mediators also play important roles in bone remodeling. The action of these substances might be complementary. For instance, TNF- α and IL-17 can act together to increase inflammatory signaling and possibly cause greater effect on osteoclastogenesis and tissue damage than either cytokine. Due to the complex nature of the cytokine network, inhibition of one mediator is likely to suppress only one aspect of the disease pathogenesis. One of the reasons for differential treatment efficacy could be due to these factors.

Therapeutic Targets

By far the most well-established therapeutic approach for treating cytokine-induced inflammation in AS is the inhibition of TNF- α . TNF inhibitors revolutionized the treatment of patients with active disease through significant improvements in symptoms such as pain and stiffness, physical function, and inflammatory markers. Through their mechanism of inhibiting TNF-induced osteoclast activation, they might even provide benefit to bone metabolism in general. Several studies have demonstrated stabilization or improvement in bone mineral density under anti-TNF treatment. On the other hand, radiographic progression seems to be a little more complicated, and anti-TNF treatment does not fully protect from syndesmophyte development. Another major therapeutic approach is targeting IL-17A. The drugs secukinumab and ixekizumab can provide a significant improvement in symptoms and objective measurements of axial disease. This mechanism targets directly one of the inflammatory pathways involved in the pathogenesis of AS. Bone density and radiographic progression in relation to IL-17 inhibitors are still being explored. Although suppression of inflammation is expected to decrease inflammatory bone loss, the effect on bone formation is still not fully elucidated.

JAK inhibitors are one of the newer treatments for axial spondyloarthritis. Due to the fact that JAKs mediate signals received by several types of cytokine receptors, simultaneous influence on several different inflammatory mediators is possible. Upadacitinib proved to be efficient in treating axial spondyloarthritis and provides an orally administered form of medication. Influence of JAKs on bone metabolism is another promising field of research. RANKL inhibition plays an important role in treatment of AS-related osteoporosis. Denosumab binds RANKL and inhibits osteoclastic bone resorption. Therefore, antiresorptive treatment in patients with AS-related osteoporosis may be justified in case of significant risk of fractures, but antiresorptive treatment must not replace control of axial inflammation. Wnt signalling pathways are promising candidates for the future. Compounds like sclerostin and DKK-1 seem especially interesting because of their influence on osteoblasts and pathological bone development. Some experiments showed a possibility of influence on syndesmophyte development using such approaches. However, clinical application is problematic because Wnt signalling is crucial for proper bone turnover and regeneration.

Relationship Between Inflammation, Osteoporosis, and Structural Progression

One of the most difficult aspects of AS is differentiating between bone loss and new bone formation. These two conditions may coexist in a patient with AS but may not necessarily be regulated by similar physiological mechanisms. Inflammatory cytokines lead to osteoclast-dependent resorption, whereas local repair and osteogenic processes contribute to new bone formation. The consequence is a complex

disease of a bone tissue characterized by simultaneous weakening and stiffening. Having spinal ankylosis is no guarantee against the development of osteoporosis; on the contrary, the risk of vertebral fractures increases greatly in a person with severe stages of spinal disease as a result of a mechanical behavior similar to that of a single big bone. This leads to an increased risk of fractures due to minor traumas.

Such a paradoxical situation proves the necessity of evaluation of bone tissue condition irrespective of any radiographic features of spinal disease. Evaluation of bone mineral density, history of vertebral fractures, level of vitamin D, amount of calcium in diet, physical activity of a patient and other risk factors for osteoporosis is necessary.

Clinical Implications

The treatment of cytokine-induced bone loss in AS requires a comprehensive approach. Inflammation should be suppressed effectively since it causes further bone loss, pain, stiffness, and functional impairment. TNF and IL-17 inhibitors are efficient for patients with active axial involvement in AS, while JAK inhibition adds an additional targeting strategy. Nevertheless, osteoporosis should be considered as a separate clinical problem. Patients with bone mineral density loss or high risks of fractures should undergo specific osteoporosis treatment. Calcium and vitamin D intake, regular physical activities and adequate pharmacotherapy can serve for bone preservation.

Physical therapy is especially necessary since controlled physical activity is helpful for preserving spinal flexibility, good posture, muscle tone and overall body performance. Physical activity can also provide mechanical stimulus required for normal bone turnover. It should be individually selected depending on severity of the disease and fracture risks. Long-term follow-up is crucial. Assessment should encompass disease activity, functional capacity, response to therapy, structural progression, and bone mineral density. Patients who have long-term disease or spinal ankylosis need special consideration for risk of vertebral fractures.

Limitations and Future Perspectives

1. Though there have been major leaps forward in understanding bone loss associated with cytokines, many questions still need to be answered. The first is about the role of inflammation in bone formation. While cytokines like TNF- α and IL-17 have been seen to play an important role in inflammation, their inhibition has not been seen to prevent structural progression. This means that other pathways are involved.
2. Bone-specific endpoints do not usually receive much attention in most clinical studies which are mostly done to address inflammatory endpoints. Bone mineral density, bone structure, vertebral fractures, and radiographic progression take time to manifest. Therefore, future clinical studies must consider these factors. Current evidence does not establish whether one biologic mechanism is consistently superior for preventing osteoporosis. TNF inhibition may improve bone density through inflammation suppression, while IL-17 inhibition may have different effects. Direct comparative studies focusing specifically on bone outcomes would be valuable.

3. Targeting Wnt pathway for therapeutic purposes is problematic. Given the necessity of the Wnt pathway in maintaining healthy bone, it might have some unintended effects. For future therapies, it will be necessary to be able to distinguish between pathologic calcification and physiologic bone formation.

The approach of precision medicine might be the key one for the future. It may be possible to find biomarkers for patients predisposed to osteoporosis, rapid progression, and certain therapeutic outcomes.

CONCLUSION

Inflammatory bone loss is an important and complex process associated with ankylosing spondylitis. In addition to inflammation and bone loss, the pathology is paradoxical in the sense that it is also characterized by bone resorption, osteoporosis, and pathological bone formation. Cytokines like TNF- α , IL-17, IL-23, IL-6, RANKL, among others, work in concert with osteoclasts, osteoblasts, osteocytes, and stroma to impair the physiological bone homeostasis. Of all these pathways, the TNF- α /RANKL pathway plays an especially important role in inflammatory osteoclastogenesis, whereas IL-17 acts on inflammatory activation and possibly bone resorption and pathological ossification. Another way of influencing the bone physiology is represented by the Wnt pathway, along with the action of its regulatory proteins, sclerostin, and DKK-1, affecting osteoblast activity and bone formation. In terms of therapy, there has been significant success achieved through the use of TNF inhibitors and IL-17 inhibitors in treating active disease. They help to control the inflammatory process that leads to the development of bone destruction. JAK inhibitors present an alternative treatment approach targeting many cytokine signaling pathways. Nevertheless, the inflammation control is not enough for the prevention of osteoporosis and pathological bone formation.

Therefore, therapy for AS will need to differentiate between the control of inflammatory disease and the management of skeletal complications. The future of therapy needs to incorporate a broader concept where there will be inhibition of inflammatory cytokines, limitation of osteoclast overactivity, maintenance of bone strength, and inhibition of pathological bone formation, without affecting normal bone healing process. More insight on the interactions between cytokines, RANKL, Wnt signaling, osteocytes, osteoblasts, and osteoclasts can be helpful in the development of such therapies. Long term clinical trials that consider disease activity, bone mineral density, fracture results, and radiographic progression will be very critical. In all, a personalized therapeutic approach combining good inflammation control and bone health will provide the best strategy.

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