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Review Article

Bone Remodeling Biomarkers and their Interplay with the Inflammatory Process in Spondyloathritis.

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Abstract

New bone formation is the main determinant of reduced spinal mobility which diminishes the long-term functional capacity of patients diagnosed with SpA. Clinical studies have shown that NSAIDs and anti-TNF-α treatment, although administered for a long time, could not prevent the progression of the disease. Therefore, a better understanding of the inflammatory process and its interplay with the molecular mechanism of new bone formation is essential to clarify the succession of events taking place. This is of highest importance for the development of new therapeutic targets in SpA.

Keywords: Bone Biomarkers; IL-23/IL-17 Axis; Spondyloarthritis

Abbreviations

AS	-	Ankylosing Spondylitis
BMP	-	Bone Morphogenetic Protein
DKK-1	-	dickkopf-1
IL	-	interleukin
NSAIDs	-	Non-Steroidal Anti-Inflammatory Drugs
OBs	-	Osteblasts
OCs	-	Osteoclasts
PG	-	Prostaglandin
SpA	-	Spondyloarthritis
TNF-α	-	Tumor Necrosis Factor α

Introduction

Spondyloarthritis (SpA) is a group of rheumatic inflammatory interrelated diseases that share common etiopathogenesis, clinical, genetic and radiological feature [1]. SpA is the result of a complex and poorly understood interplay between susceptibility genes, microbiota and socio-professional factors that can drive inflammation and new bone formation. SpA includes Ankylosing Spondylitis (AS), reactive arthritis, psoriatic arthritis, inflammatory bowel disease related arthritis and undifferentiated SpA.

The first symptoms usually occur in the second and third decade of life and it is thus an important cause of disability for the active population. The main symptom in case of axial involvement is the insidious onset of low back pain. Pain improves while walking and it is accompanied by morning stiffness and nocturnal exacerbation. Disease can progress to total damage of the spine through the process of new bone formation, resulting in a bamboo spine. In case of peripheral involvement, the main symptoms are either joint swelling, manly large joints in the lower limbs or pain and inflammation at the insertion of the tendons/ligaments (enthesitis). A less common peripheral manifestation is dactylitis (the swelling of a finger or a toe into a sausage shape). Extra - articular manifestations may occur in a number of patients whenever during the course of the disease as acute anterior uveitis, inflammatory bowel disease or psoriasis.

The main concern in the evolution SpA is to prevent disease progression towards spinal ankylosis, as it was demonstrated that new bone formation independently contributes to the burden of the disease [2]. Patients with advanced spinal ankylosis, present a significant impairment in physical function and quality of life thus,

having a reduced socio-professional insertion. Although insights were obtained for the molecular mechanisms regulating the pathophysiological process of inflammation and bone formation, new pharmacological targets are difficult to be defined because the scarce replication regarding bone remodeling biomarkers in SpA patients. Therefore, it would be important identify biomarkers which can reflect the underlying inflammation and more importantly which are able to predict the structural damage in order to select proper patients for potent treatment.

Several biomarkers are known to be related to bone turnover. Thus, it is known that activation of Osteoclasts (OCs) plays an important role in bone loss and the development of erosions. In contrast, inhibition of OCs and activation of Osteoblasts (OBs) are linked with new bone formation and ossification. Osteoprotegerin (OPG), which is produced by OBs, inhibits human receptor activator of nuclear factor-κβ ligand (RANKL) and plays an important role in bone formation. There is evidence which suggests that lower OPG levels and higher sRANKL/OPG ratio characterize AS patients [3]. In the last years, various components of the Wnt signaling pathways were found to be involved in maintaining bone mass. The most-studied Wnt inhibitors were sclerostin secreted exclusively by osteocytes and dickkopf-1 (Dkk-1) secreted by OBs and osteocytes with consequent reduction of bone formation. Loss of signaling through DKK-1 and sclerostin increases bone mass. Cross-sectional as well as prospective studies have found lower DKK-1 levels in patients with AS compared to healthy controls [3,4]. In their study, Heilad et al. found that functional DKK-1 [5] levels were significantly higher in patients with no syndesmophyte growth compared with those with syndesmophyte growth [6].

The evidence published so far has shown that Tumor Necrosis Factor- α (TNF-α) stimulates DKK-1. Thus, inhibition of the inflammatory process by TNF-α blocking agents like Infliximab, Etancercept, Adalimumab, Golimumab and Certolizumab may promote the stimulation of the Wnt pathway and signaling through growth factors like Bone Morphogenetic Protein (BMP), which will lead to OBs differentiation and new the bone formation [6].

The mechanism of action of sclerostin is similar to DKK-1, blocking signaling through the osteoformatory Wnt pathway, having thus an effect on BMP-mediated signaling. Furthermore, numerous non sclerostin secreting osteocytes with normal osteocyte density were found in patients with AS [7]. That could show the alteration of osteocyte function in patients with AS. There are studies in which low serum levels of sclerostin have been correlated with syndesmophytes formation. Radiological progression in AS was associated with significantly low levels of sclerostin. As a mechanism involved in the development syndesmophytes, persistent inflammation in the spine corners (cortical bone) associated with low sclerostin was suggested, as the authors reported persistently reduced sclerostin levels in patients with a high disease activity in spite of anti TNF-α treatment [8].

Hence, low levels of sclerostin appear to be associated with new bone formation. But, it is unclear whether syndesmophytes are consecutively produced or the decrease in scleostin level is a response to their presence [9]. Further studies might determine whether these changes could be markers of interplay inflammation and bone formation during the treatment. A very recent study confirmed the presence of significantly lower serum levels of sclerostin in patients with AS compared to healthy controls, but did not find any correlations with disease activity, anti-TNF-α treatment or with radiographic damage. This result can stand for the hypothesis that inflammation and new bone formation are independent processes and sclerostin levels are not consequently influenced by the presence of inflammation [9]. Recently, a systematic review did not suggest the role of sclerostin as a potential biomarker of structural damage, due to the lack of significant differences in serum levels of sclerostin between cases and controls [10].

Additional evidence shows the existence of trans- signaling between Wnt pathway and Prostaglandin (PG), with reduced levels of DKK-1 and sclerostin by increased levels of PGE2 with increased transmission of the Wnt pathway. This could imply that osteoproliferation (Wnt pathway) may be inhibited by substances that block the effect of prostaglandin E2 (PGE2), such as **Non-Steroidal Anti-Inflammatory Drugs** (NSAIDs) [11].

This would justify the use of NSAIDs to inhibit osteoproliferation in AS [12]. Furthermore, differences in selective and non-selective Cyclooxygenase (COX) inhibitors on bone formation have been described. In several models of fracture healing, celecoxib and rofecoxib (selective COX-2 inhibitors) showed stronger impairment on fracture healing than indomethacin (non-selective COX inhibitor) [13]. However, there was no clear difference between celecoxib and indomethacin in the prevention of heterotopic ossification after total hip replacement in one investigation while in another study celecoxib was superior to ibuprofen (non-selective COX inhibitor) for the same indication [13]. Additionally, celecoxib but not non-selective COX inhibitors were found to induce apoptosis in OBs-an activity that could be relevant in bone formation in AS. In addition, there is accumulating evidence that celecoxib also affects signaling pathways independent of COX-2 and PGE2 inhibition [13]. Such COX-2 independent activities that primarily affect cell proliferation and survival might result in different effects on joint remodeling including new bone formation. Moreover, the differences in COX-independent mechanisms may have consequences for the specific use of these drugs in AS.

Another theory proposes that the PGE2 released in inflammatory foci activates resident antigen presenting cells and results in the expression of interleukin-23 (IL-23) at the expense of IL-12, resulting in a change of the cellular response

to Th17, followed by recruitment and activation of neutrophils in order to maintain the chronic inflammatory process. PGE2 has been reported to have also anti-inflammatory effects, action mainly mediated through the release of IL-10 by the activated T and dendritic / macrophages cells [14]. On the other hand, there is evidence indicating the increased involvement of the innate immune system cells, such as macrophage, neutrophil and mast cell in the generation and maintenance of the inflammatory process in SpA [15]. Alteration of the innate immune response may be related to the non-antigen presenting function of HLA-B27, by inducing a defective folding response of the protein, triggered by mechanical stress or bacterial infections. Cells of the innate immune system appear to be the main producers of pro-inflammatory (TNF, IL-1, IL-23, IL-17) and anti-inflammatory (IL-10) cytokines in SpA [16].

A key research area is nowadays the IL23/IL-17 axis since genetic association studies in AS patients showed the potential role in chronic inflammation of the IL23 receptor [17]. The involvement of IL-23/IL-17 axis in the remodeling process is also supported by in vitro models (eg: IL-23 increased production due to defective folding of HLA-B27) [18], in animal models (eg: the enhancement of IL-17 production in HLA-B27 transgenic rats) [19] and by human studies (eg: the expansion of IL-17 producing cells of the innate immunity) [20], thus indicating a new pharmacological target.

IL-23 is a heterodimeric cytokine that binds to β1 Transmembrane Receptor (IL-12Rβ1). It contains the p40 disulfide subunit and induces the JAK / STAT mediated intracellular signaling pathway [21]. Cytokine IL-23 together with IL-21 and Tumor Growth Factor β (TGFβ) stimulate the production of the lymphocyte Th17 CD4 + population which will generate IL-17A, IL-17F, IL-22, TNF-α and IL-1β [22,23]. The importance of IL-17 (or IL-17A) in the generation and perpetuation of the inflammatory response lies in the fact that this cytokine is produced by both Th17 CD4 + lymphocytes and other cell types such as neutrophils, mast cells, NK cells and T γδ cells [24,25]. Furthermore, in the study published by Appel et al in 2011 the cell lines responsible for IL-17 production in patients with SpA were identified as belonging to innate immunity [26].

In addition, research has shown that synovial joints of patients with SpA present increased amounts of IL-17 [27,28]. It was demonstrated that IL-17 is functionally active in SpA, operating synergistically with other cytokines by controlling the release of cytokines and metalloproteases involved in pathogenesis of the disease [29]. In the recent years, new molecules capable of interfering with signal transition on the IL-23 / Th-17 axis such as Ustekinumab, an IL-12 / IL-23 inhibitor, Secukinumab and Ixekizumab, IL-17A inhibitor were approved for the treatment of SpA and /or psoriasis.

Conclusion

In conclusion, a better understanding of the inflammatory process and its relationship with the molecular mechanism of bone remodeling is essential to clarify the sequence of events that take place, in order to develop new therapeutic targets in SpA.

Conflict of Interest

The authors declare no any economic interest or any conflict of interest.

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