Rheumatology International (2020) 40:2057–2063
https://doi.org/10.1007/s00296-020-04708-z

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Bone turnover biomarkers, disease activity, and MRI changes of sacroiliac joints in patients with spondyloarthritis

Oleg Iaremenko[1] · Iuliia Shynkaruk[1] · Dmytro Fedkov[1] · Kateryna Iaremenko[2] · Liubov Petelytska[1]

Received: 10 August 2020 / Accepted: 16 September 2020 / Published online: 26 September 2020

Abstract

The lack of valid biomarkers in patients with spondyloarthritis (SpA) requires searching for additional options to increase sacroiliac joint (SIJ) evaluation effectiveness. We assessed the serum levels of bone turnover markers and their relationships with active and chronic changes in SIJs using magnetic resonance imaging (MRI), indices, and laboratory parameters of disease activity in SpA patients. 102 patients with SpA and 15 healthy subjects were included. Testing of serum levels of transforming growth factor-beta (TGF-β1), Wnt3, sclerostin, and Dickkopf-1 (Dkk-1) was conducted. Active inflammatory lesions in SIJs were evaluated using Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SIJ score, and chronic changes using the Danish scoring method. Bath Ankylosing Spondylitis Disease Activity Index, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Ankylosing Spondylitis Disease Activity Scores with CRP, and ESR were used to assess disease activity. Serum levels of Dkk-1, TGF-β1, and sclerostin were significantly lower in SpA patients compared to healthy controls. The serum levels of Dkk-1 positively correlated with CRP. Dkk-1 had a significant negative correlation with Danish score. The sclerostin serum level had a weak negative correlation with the active inflammatory MRI SIJ lesions. There were positive correlations between TGF-β1 and sclerostin with Dkk-1, and negative correlation between Wnt3 and sclerostin. Dkk-1 positively correlated with CRP and negatively with chronic SIJ changes by Danish score. Sclerostin negatively correlated with the active SIJ lesions by SPARCC. This suggests that Dkk-1 and sclerostin are the most promising candidates to reveal inflammation and bone turnover in patients with SpA.

Keywords Spondyloarthritis · Biomarkers · Magnetic resonance imaging · Sacroiliac joint

Introduction

Diagnosis of spondyloarthritis (SpA) is often difficult, especially in axial form, when no manifested sign of the disease can be detected by the consulting physician [1]. In recent years, magnetic resonance imaging (MRI) has been one of the main diagnostic tools that are used in patients with SpA [2]. The advantage of MRI scans over X-rays lies in its ability to detect early changes in sacroiliac joints (SIJs), which precede structural changes determined by standard X-ray technique.

There are currently insufficient data regarding the relationship between the biomarkers that correlate with disease activity (calprotectin, vasoactive endothelial growth factor, and citrullinated metalloproteinase degraded fragment of vimentin) and MRI inflammation [3]. That is why, there is an actual demand for researching biomarkers which could reflect disease activity and MRI changes in SIJs in patients with SpA. Recent research suggests that the inflammatory

✉ Dmytro Fedkov
fedkovdmytro@gmail.com

Oleg Iaremenko
o.b.iaremenko@gmail.com

Iuliia Shynkaruk
iuliia.shynkaruk@gmail.com

Kateryna Iaremenko
k.iaremenko@gmail.com

Liubov Petelytska
l.petelytska@gmail.com

[1] Department of Internal Medicine #3, Bogomolets National Medical University, T. Shevchenko Boulevard, 13, Kiev 01601, Ukraine

[2] Central Laboratory Department, Olexandrivska City Hospital, Kiev 01601, Ukraine

damage of SIJs in SpA patients is capable of transforming into new bone formations, followed by fatty modification [4, 5]. In light of these findings, it is important to evaluate not only inflammatory but also chronic MRI changes in SIJs, as well as bone turnover biomarkers. These two reinforced, but opposite processes present themselves as both diagnostic and therapeutic issues.

Dickkopf-1 (Dkk-1), sclerostin, and WNT3 (wingless-type of mouse mammary tumor virus integration site family, member 3) are markers of bone metabolism. The canonical Wnt pathway (or Wnt/β-catenin pathway) is the pathway that induces the accumulation of β-catenin in the cytoplasm and its possible translocation into the nucleus to act as a coactivator of transcription factors belonging to the TCF/LEF family. The transmission of signals through Wnt/β-catenin system is usually the main way to regulate the formation of new bone with an artificial increase in bone mineral density, accompanied by trabecular bone tissue loss. Wnt proteins may also play a role in the osteoblastic new bone formation in SpA. It has recently been found that various components of Wnt signaling molecules are involved in maintaining bone mass [6]. Wnt3 is the most bone-specific protein of Wnt/β-catenin signaling pathway. This pathway regulates the differentiation, proliferation, and synthesis of the bone matrix, as well as the transmission of mechanical stress signals [7]. One study has shown that SpA patients had higher WNT3 serum levels compared to the healthy controls [8]. In response to mechanical overload, activation of Wnt/β-catenin in osteocytes leads to a decrease in the expression of negative pathway regulators such as Dkk-1 and sclerostin, which realize their effects by binding Wnt to its coreceptors [9]. However, under increasing load, long-term sclerostin deficiency may lead to bone formation activation [10]. Activation of Wnt signaling pathway by blocking Dkk-1 encourages the formation of osteophytes in peripheral joints [11]. Mechanical loading of osteocytes induces the stimulation of the bone morphogenetic protein (BMP) [12], while a decrease in Dkk-1 and sclerostin levels could activate Wnt and BMP signaling [7]. It has recently been shown that low serum levels of sclerostin [13] and Dkk-1 [14] are associated with the formation of new syndesmophytes in SpA patients.

There are inconsistent results across different studies of Dkk-1 serum levels in SpA patients and healthy control subjects. Thus, some studies demonstrated that Dkk-1 serum levels in SpA patients were higher than those in control subjects [15], while others reported that patients with SpA had lower levels of Dkk-1 compared to the controls [16, 17]. Therefore, additional extended research is needed to study the pathophysiological role of Dkk-1 in patients with SpA.

It has been reported that serum levels of sclerostin were lower in patients with SpA compared to control subjects [17, 18]. It is important to note that there are studies on the levels of Dkk-1 and sclerostin in the patients that did and did not receive inhibitors of tumor necrosis factor, as well as in the patients with active and inactive disease [17].

There also exist research projects looking at the association between Dkk-1 levels and disease duration in SpA patients [19].

Transforming growth factor-beta (TGF-β1) is a multifunctional cytokine that inhibits lymphocytes and stimulates chondrocytes, fibroblasts, and osteoblasts [20]. Wnt/β-catenin signaling pathway works in parallel with TGF-β, and the inactivation of TGF-β signaling can cause the expression of members of the Wnt/β-catenin and vice versa [21]. Hybridization studies of biopsies from SIJs have identified increased expression of TGF-β mRNA, particularly near the new bone formation, but not in the inflammatory infiltrates [22]. Production and activation of TGF-β are stimulated by hyperthermia and exercise [23–25]. Sclerostin isolates BMP through competitive inhibition contact and avoids connection with TGF-β receptors [26]. TGF-β1 serum level has been reported to be increased in patients with SpA [27–29]. TGF-β is likely to play an important role in new bone formation in patients with SpA.

This study was designed to investigate the level of biomarkers (Dkk-1, sclerostin, TGF-β1, and WNT3) and their association with MRI changes in SIJs and with disease activity parameters in patients with SpA.

Methods

Patients

102 patients with SpA and 15 healthy control subjects matched for gender and age were enrolled. Inclusion criteria were the following: participants must have been at least 18 years of age, who would provide written informed consent and who have been clinically diagnosed with SpA by the rheumatologist and have fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial [30] and peripheral [31] SpA. Exclusion criteria were: a history of the other rheumatic diseases, spinal surgery, and spinal tumor.

Study design

This observational descriptive cross-sectional monocentric study was conducted at the departments of internal medicine #3 of Bogomolets National Medical University between Feb 2016 and Oct 2018. Out of 105 identified patients, 3 belonged to the "dropout" group (3 patients did not fulfill ASAS criteria). The remaining 102 patients underwent the necessary study procedures during Visit 1. All assessment procedures were conducted simultaneously, except for MRI and laboratory tests excluding biomarkers, which were

considered eligible if performed during Visit 1 ± 7 days. After the informed consent was signed and until the end of all study procedures, therapy changes were not allowed. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the appropriate institutional review boards (Local Ethic Committee of Bogomolets National Medical University, protocol #58, dated 26 Feb 2016).

Disease activity assessment

Disease activity was measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, scored from 0 to 10 cm) [32], C-reactive protein (CRP, mg/l, ULN—6), erythrocyte sedimentation rate (Westergren ESR, mm/hr), Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), and with ESR (ASDAS-ESR) [33].

Biomarkers assessment

Serum samples of TGF-β1 (Demeditec Diagnostics GmbH), WNT3 (Cloud-Clone Corp.), sclerostin (Biomedica), and Dkk-1 (Biomedica) were analyzed using a commercially available ELISA kit (iMark Mikroplate Reader, BIO RAD, USA) according to the manufacturer's instructions. Fasting blood samples were collected into tubes containing serum separation gel (serum separator clot activator) that isolates the clot from the serum in whole blood specimens. Samples were centrifuged at 2000 rpm for 10 min.

MRI assessment

For MRI scan of the SIJ, 1.5 T MRI scanner (Magnetom Avanto, SIEMENS, Germany) was used. The SIJ MRI images of the patients were evaluated by one independent reader and scored using the Spondyloarthritis Research Consortium of Canada (SPARCC) method for evaluation of active inflammatory lesions (score 0–72) [34] and the Danish scoring method (score 0–48) for chronic changes [35]. The SIJ MRI was performed in 81 patients, but only 67 were included in the analysis due to the time frame issues.

Statistical analysis

IBM SPSS 22.0 software was used for statistical analysis. Demographics and clinical characteristics were described as numbers (%) and as median (min–max). All correlations were evaluated by Spearman's correlation test. The values were compared between groups of SpA patients and healthy controls using a nonparametric test (Mann–Whitney). p value ≤ 0.05 was considered to represent statistical significance.

Results

Patients

One hundred and two SpA patients were included in the study: 67 (65.7%) male and 35 (34.3%) female patients, ranging in age from 20 to 74 (38.1 ± 11.2) years. 40 patients fulfilled the ASAS axial SpA criteria and 62 patients fulfilled the peripheral SpA criteria (39.2% vs 60.8%). The duration of disease ranged from 0.6 to 480 months. Among 75 patients, whose human leukocyte antigen B27 (HLA-B27) status was previously defined at 65, were HLA-B27-positive (86.7%). Nonsteroidal anti-inflammatory drugs were taken by 75.5% of patients, corticosteroids (CS)—by 37.3%, synthetic disease-modifying antirheumatic drugs (DMARDs) (methotrexate, sulfasalazine, or leflunomide)—by 54.9%, biologic DMARDs (adalimumab, etanercept, infliximab, and golimumab)—by 15.7%, and previously using intra-articular CS—by 21.6% of patients. 7.84% of patients did not receive any medications.

Disease activity

According to BASDAI score, disease activity among all SpA patients was high: 4.25 (0.34–9.4), mean ± SD—4.53 ± 1.86, while the level of laboratory activity (by ESR) turned out to be low: ESR was 20 (2–99), mean ± SD—27.1 ± 22.1. However, CRP (~ 3 times ULN) has better displayed the clinical activity degree: 8 (0–202), mean ± SD—20.9 ± 31.5. At the same time, the mean values of ASDAS-CRP and ASDAS-ESR were comparable: 2.99 (0–5.35), mean ± SD—3.07 ± 1.07, and 2.86 (0.96–5.25), mean ± SD—3.00 ± 0.96 respectively (Table 1). The scores of active and chronic MRI changes were high: SPARCC was 21 (0–56), mean ± SD—22.5 ± 11.9, Danish score was 18 (0–40), and mean ± SD—20.1 ± 9.35.

Table 1 Disease activity parameters

Parameter	Median (min–max)
CRP (mg/l)	8.26 (0–202)
ESR (mm/h)	20 (2–99)
BASDAI	4.25 (0.34–9.4)
ASDAS-CRP	2.99 (0–5.35)
ASDAS-ESR	2.86 (0.96–5.25)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score with CRP, *ASDAS-ESR* Ankylosing Spondylitis Disease Activity Score with ESR

SpA patients vs healthy control subjects

The patients with SpA had significantly lower serum levels of Dkk-1 ($p < 0.001$), TGF-β1 ($p < 0.001$), and sclerostin ($p < 0.001$) compared with the healthy controls (Table 2). The differences in serum levels of WNT3 between SpA patients and controls were not significant ($p = 0.059$).

Correlations

To determine the relationship between biomarkers' serum levels with laboratory parameters, clinical indices, and MRI imaging scores, correlation analysis was performed (Tables 3 and 4). The serum Dkk-1 concentration had weak positive correlation with CRP ($r = 0.216$, $p = 0.029$). There was no significant correlation between other disease activity parameters and bone turnover biomarkers.

Dkk-1 had a weak negative correlation with the chronic MRI changes in SIJs ($r = -0.293$, $p = 0.018$), but not with the active MRI imaging score. The sclerostin serum level was negatively correlated with the SPARCC score ($r = -0.266$, $p = 0.030$). There were no significant correlations between the serum TGF-β1 and WNT3 concentrations with active and chronic MRI imaging scores.

At the same time, different biomarkers exhibited significant correlations between themselves: positive correlations of Dkk-1 with TGF-β1 and sclerostin, and negative correlations between WNT3 and sclerostin (Table 5).

Table 2 Serum levels of bone turnover biomarkers in SpA patients and the controls

Biomarker	SpA patients, median (min–max)	Healthy controls, median (min–max)	*p*
TGF-β1 (pmol/l)	248.9 (3.03–998.2)	437.1 (320.0–632.7)	< 0.001
WNT3 (ng/ml)	4.04 (0.14–19.5)	28.2 (2.44–5.58)	0.059
Sclerostin (pmol/l)	18.5 (0.32–75.9)	120.4 (17.1–52.2)	< 0.001
Dkk-1 (pmol/l)	40.4 (2.76–156.2)	120.4 (33.0–140.4)	< 0.001

SpA spondyloarthritis, *TGF-β1* transforming growth factor-beta, *Dkk-1* Dickkopf-1

Table 4 Correlations of bone turnover biomarker's serum levels with MRI imaging scores of active and chronic changes in SIJ

Biomarker	SPARCC		Danish score	
	R	*p*	*r*	*p*
TGF-β1	−0.178	0.150	−0.132	0.294
WNT3	−0.018	0.884	0.116	0.359
Sclerostin	−0.265*	0.030	−0.171	0.174
Dkk-1	−0.104	0.404	−0.293*	0.018

SIJ sacroiliac joints, *SPARCC* Spondyloarthritis Research Consortium of Canada, *TGF-β1* transforming growth factor-beta, *Dkk-1* Dickkopf-1

*$p < 0.05$

Discussion

In our study, the serum levels of Dkk-1 were significantly lower in SpA patients in comparison with the healthy controls that coincide with other studies [16, 17]. Daoussis et al. suggested an insignificant inhibitory role of Dkk-1 to Wnt activation in patients with SpA in comparison to the healthy controls [36]. Low levels of serum Dkk-1 in patients with SpA indicate the activation of Wnt signaling and could be a reason for the compensatory response to the deficiency of sclerostin. The activation of Wnt may induce the neo-osteogenesis in the joints with inflammation and increase the number of osteophytes [11] that lead to the destruction of the joint architecture.

We found that the serum TGF-β1 levels were lower in patients with SpA in comparison to the healthy controls. These findings, however, do not match the results of other studies, which described the significantly higher expression of TGF-β1 in SpA patients [27–29]. This discrepancy could be associated with possible osteoporosis or osteopenia, as demonstrated by Akinci et al. in their study [37] which shows that the level of TGF-β1 was significantly lower in

Table 3 Correlations of bone turnover biomarker's serum levels with disease activity parameters

Biomarker	ESR, *r* (*p*)	CRP, *r* (*p*)	ASDAS-CRP, *r* (*p*)	ASDAS-ESR, *r* (*p*)	BASDAI, *r* (*p*)
TGF-β1	0.174 (0.079)	0.153 (0.124)	0.057 (0.567)	0.083 (0.408)	0.044 (0.658)
WNT3	0.101 (0.313)	0.118 (0.236)	0.060 (0.547)	0.053 (0.597)	0.054 (0.589)
Sclerostin	−0.035 (0.724)	−0.146 (0.142)	−0.162 (0.104)	−0.044 (0.664)	−0.025 (0.803)
Dkk-1	0.118 (0.236)	0.216* (0.029)	0.191 (0.054)	0.111 (0.265)	0.084 (0.402)

CRP C-reactive protein, ESR erythrocyte sedimentation rate, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score with CRP, *ASDAS-ESR* Ankylosing Spondylitis Disease Activity Score with ESR, *TGF-β1* transforming growth factor-beta, *Dkk-1* Dickkopf-1

*$p < 0.05$

Table 5 Correlations between bone turnover markers

Biomarker	TGF-β1, *r* (*p*)	WNT3, *r* (*p*)	Sclerostin, *r* (*p*)	Dkk-1, *r* (*p*)
TGF-β1	–	−0.099 (0.323)	0.141 (0.156)	0.298* (0.002)
WNT3	−0.277 (0.323)	–	−0.230* (0.020)	−0.143 (0.152)
Sclerostin	0.141 (0.156)	−0.230* (0.020)	–	0.285* (0.004)
Dkk-1	0.298* (0.002)	−0.143 (0.152)	0.285* (0.004)	–

TGF-β1 transforming growth factor-beta, *Dkk-1* Dickkopf-1

*$p < 0.05$

patients with osteoporosis when compared with healthy individuals. This area may require further in-depth studies.

The serum levels of sclerostin were significantly lower in the patients with SpA, which match the results of other studies [17, 18].

Serum levels of WNT3 did not differ between SpA and control groups. One prior study [8] reported that patients with SpA had significantly higher serum levels of WNT3 compared with the controls and that WNT3 may be a marker for osteoproliferation in SpA patients. Another study reported that patients treated with TNF inhibition had higher serum levels of Wnt. The resolution of inflammation following the anti-TNF treatment has been associated with new bone formation in SpA. It has been hypothesized that this could be caused by increased Wnt signaling and that TNF-α acts as a brake on bone formation by stimulating the expression of the Wnt antagonist Dkk-1. According to the 2019 review, there have been no recent studies that have attempted to clarify discrepancies in WNT3 serum levels between SpA patients and healthy controls [3].

Dkk-1 was positively correlated with CRP and could be related to systemic inflammation, but not directly to the disease activity measured with indices. In our study, no other biomarkers were correlated with clinical and laboratory parameters of disease activity, which is similar to other studies that showed the absence of significant correlations of disease activity with TGF-β [27, 38, 39], WNT3 [8], and sclerostin [17].

Dkk-1 was also correlated with chronic MRI SIJ changes, but not with active SIJ lesions. In one recent study of the correlation between Dkk-1 and MRI pathological changes in the spine and the SIJ, it was detected that Dkk-1 concentration is significantly correlated with the spinal bone marrow edema scores but not with fat infiltration scores, and no significant correlation between the serum Dkk-1 concentration, and the sacroiliac MRI bone marrow edema, fat infiltration, bone erosion, and backfill was detected [2]. These results are the reason for further in-depth study with an MRI screening for all parts of the spine.

Sclerostin serum levels negatively correlated with active MRI SIJ lesions by SPARCC score. TGF-β1 and WNT3 did not show any significant correlation with active or chronic changes. We did not find any other study that would describe the correlation between MRI SIJ and sclerostin, TGF-β1, or WNT3.

However, positive correlations of Dkk-1 with TGF-β1 and sclerostin, as well as negative correlations of WNT3 with sclerostin have been found. Similar results were reported in two studies in which positive correlations between sclerostin and Dkk-1 were found [8, 40]. Results of such a relationship between these biomarkers could reflect their interdependence.

Our study had some limitations. Evaluated procedures (MRI, blood sampling for biomarkers, and assessment of disease activity indices) were not performed on the same day, which could affect the evaluation of correlations. To reduce the influence of these time frame discrepancies, specified time frames for certain procedures were set up, ensuring compatibility of results. We also did not evaluate bone mineral density in patients and the control group, so the influence of this factor on the results was not taken into account. Also, since the study was non-invasive and did not impose requirements on therapy before inclusion in the study, the possible effects of medications (TNF inhibitors and CS especially) on the studied parameters were not considered. The main limitation of our study was the absence of MRI screening for the spine, since the conduct of spine MRI screening was not necessary for the majority of patients under the standards for diagnosis and management of this group of patients. Also, one study confirms that lesions "typical of axial SpA" can also be observed in both patients with mechanical chronic back pain without axial SpA and in an axial SpA cohort [41]. Active and structural SIJ lesions by all modalities remain the most valuable for diagnosis. Another study has revealed that combined spine and SIJ MRI added little incremental value compared with SIJ MRI alone for diagnosing patients with axial non-radiographic SpA and enhancing confidence in this diagnosis [42]. The absence of these data could potentially limit our ability to find correlations between MRI changes and laboratory parameters for patients with the dominant spinal but not SIJ lesions. Our study detected a relationship between Dkk-1 and chronic MRI SIJ changes, but not with active SIJ lesions. In contrast, the results of Z Zhao et al.'s study revealed a correlation of Dkk-1 with the spinal bone marrow edema scores but not with chronic changes, and there was no correlation of Dkk-1 with active and chronic SIJ MRI lesions revealed [2].

This case requires further depth study with evaluation of the relationships between biomarkers with spine MRI.

Conclusion

Currently, there are limited data regarding the correlation of biomarkers and disease activity, particularly MRI changes in SIJs, in patients with SpA. We analyzed serum levels of Dkk-1, sclerostin, TGF-β1, and WNT3 and their relationships with clinical and laboratory parameters of disease activity and MRI SIJ changes in 102 patients with SpA. We found that Dkk-1 positively correlates with CRP and negatively with chronic SIJ MRI. Sclerostin negatively correlates with active MRI SIJ lesions. Dkk-1 and sclerostin better reflect the SIJ MRI changes (both chronic and active) compared to TGF-β1 and Wnt3. Thus, among the investigated biomarkers, Dkk-1 and sclerostin are the most likely candidates for future research of their relationship with inflammation and bone turnover in patients with SpA.

Author contributions All authors participated in the analysis and interpretation of the data, reviewed and provided feedback on the draft manuscript, and made the decision to submit the manuscript for publication. All authors vouch for the completeness and accuracy of the data and analyses. Material preparation, literature search, and data analysis were performed by OI, IS, DF, and LP. Laboratory methods and specimen handling for biomarkers were performed by KI. The first draft of the manuscript was written by DF and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding We did not have any financial support.

Compliance with ethical standards

Conflict of interest Oleg Iaremenko, Iuliia Shynkaruk, Dmytro Fedkov, Kateryna Iaremenko, and Liubov Petelytska declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the appropriate institutional review boards (Local Ethic Committee of Bogomolets National Medical University, protocol #58, 26 Feb 2016). Authors fulfilled the ICMJE authorship criteria.

Informed consent Written informed consent was obtained from all patients prior to study start.

References

1. Lukas C, Cyteval C, Dougados M, Weber U (2018) MRI for diagnosis of axial spondyloarthritis: major advance with critical limitations 'Not everything that glitters is gold (standard)'. RMD Open 4(1):e000586. https://doi.org/10.1136/rmdopen-2017-000586
2. Zhao Z, Wang G, Wang Y et al (2019) Correlation between magnetic resonance imaging (MRI) findings and the new bone formation factor Dkk-1 in patients with spondyloarthritis. Clin Rheumatol 38(2):465–475. https://doi.org/10.1007/s10067-018-4284-y
3. Maksymowych WP (2019) Biomarkers for diagnosis of axial spondyloarthritis, disease activity, prognosis, and prediction of response to therapy. Front Immunol 10:305. https://doi.org/10.3389/fimmu.2019.00305
4. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych W (2011) Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum 63(8):2215–2225. https://doi.org/10.1002/art.30393
5. Maksymowych W, Chiowchanwisawakit P, Lambert R (2010) TNF blocking agents promote resolution of structural lesions in patients with spondyloarthritis. Ann Rheum Dis 69:262
6. Xie W, Zhou L, Li S, Hui T, Chen D (2016) Wnt/β-catenin signaling plays a key role in the development of spondyloarthritis. Ann N Y Acad Sci 1364(1):25–31. https://doi.org/10.1111/nyas.12968
7. Bonewald LF, Johnson ML (2008) Osteocytes, mechanosensing and Wnt signaling. Bone 42(4):606–615. https://doi.org/10.1016/j.bone.2007.12.224
8. Klingberg E, Nurkkala M, Carlsten H, Forsblad-d'Elia H (2014) Biomarkers of bone metabolism in ankylosing spondylitis in relation to osteoproliferation and osteoporosis. J Rheumatol 41(7):1349–1356. https://doi.org/10.3899/jrheum.131199
9. Neve A, Corrado A, Cantatore FP (2012) Osteocytes: central conductors of bone biology in normal and pathological conditions. Acta Physiol 204(3):317–330. https://doi.org/10.1111/j.1748-1716.2011.02385.x
10. Morse A, McDonald MM, Kelly NH et al (2014) Mechanical load increases in bone formation via a sclerostin-independent pathway. J Bone Miner Res 29(11):2456–2467. https://doi.org/10.1002/jbmr.2278
11. Diarra D, Stolina M, Polzer K et al (2007) Dickkopf-1 is a master regulator of joint remodeling. Nat Med 13(2):156–163. https://doi.org/10.1038/nm1538
12. Santos A, Bakker AD, Willems HM et al (2011) Mechanical loading stimulates BMP7, but not BMP2, production by osteocytes. Calcif Tissue Int 89(4):318–326. https://doi.org/10.1007/s00223-011-9521-1
13. Appel H, Ruiz-Heiland G, Listing J et al (2009) Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. Arthritis Rheum 60(11):3257–3262. https://doi.org/10.1002/art.24888
14. Sieper J, Appel H, Rudwaleit M et al (2010) Inverse correlation between serum levels of dickkopf 1 (DKK 1), and new bone formation in ankylosing spondylitis patients. Ann Rheum Dis 69(3):442
15. Zhang L, Ouyang H, Xie Z, Liang ZH, Wu XW (2016) Serum DKK-1 level in the development of ankylosing spondylitis and rheumatic arthritis: a meta-analysis. Exp Mol Med 48(4):e228. https://doi.org/10.1038/emm.2016.12
16. Kwon SR, Lim MJ, Suh CH et al (2012) Dickkopf-1 level is lower in patients with ankylosing spondylitis than in healthy people and is not influenced by anti-tumor necrosis factor therapy. Rheumatol Int 32(8):2523–2527. https://doi.org/10.1007/s00296-011-1981-0
17. Ustun N, Tok F, Kalyoncu U et al (2014) Sclerostin and Dkk-1 in patients with ankylosing spondylitis. Acta Reumatol Port 39(2):146–151
18. Perrotta FM, Ceccarelli F, Barbati C et al (2018) Serum sclerostin as a possible biomarker in ankylosing spondylitis: a case-control study. J Immunol Res 2018:9101964. https://doi.org/10.1155/2018/9101964
19. Rubio Vargas R, Melguizo Madrid E, González Rodríguez C et al (2017) Association between serum dickkopf-1 levels and disease

duration in axial spondyloarthritis. Reumatol Clin 13(4):197–200. https://doi.org/10.1016/j.reuma.2016.04.013
20. Roberts AB, Sporn MB (1990) Peptide growth factors and their receptors. In: Handbook of experimental pharmakology. Springer-Verlag, New York
21. Guo Y, Xiao L, Sun L, Liu F (2012) Wnt/beta-catenin signaling: a promising new target for fibrosis diseases. Physiol Res 61(4):337–346. https://doi.org/10.33549/physiolres.932289
22. Braun J, Bollow M, Neure L et al (1995) Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. Arthritis Rheum 38(4):499–505. https://doi.org/10.1002/art.1780380407
23. Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S (1999) Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. JAMA 281(18):1722–1727. https://doi.org/10.1001/jama.281.18.1722
24. Gavin TP, Spector DA, Wagner H, Breen EC, Wagner PD (2000) Nitric oxide synthase inhibition attenuates the skeletal muscle VEGF mRNA response to exercise. J Appl Physiol 88:1192–1198. https://doi.org/10.1152/jappl.2000.88.4.1192
25. Barcellos-Hoff MH, Derynck R, Tsang ML, Weatherbee JA (1994) Transforming growth factor-beta activation in irradiated murine mammary gland. J Clin Invest 93(2):892–899. https://doi.org/10.1172/JCI117045
26. Chen G, Deng C, Li YP (2012) TGF-β and BMP signaling in osteoblast differentiation and bone formation. Int J Biol Sci 8(2):272–288. https://doi.org/10.7150/ijbs.2929
27. Vaez F, Farazmand A, Shaaheen S et al (2017) Upregulation of transforming growth factor-B1 gene in ankylosing spondylitis patients. Rheum Res 2(3):103–107. https://doi.org/10.22631/rr.2017.69997.1026
28. Yang C, Ding P, Wang Q et al (2016) Inhibition of complement retards ankylosing spondylitis progression. Sci Rep 6:34643. https://doi.org/10.1038/srep34643
29. Howe HS, Cheung PL, Kong KO et al (2005) Transforming growth factor beta-1 and gene polymorphisms in oriental ankylosing spondylitis. Rheumatology 44(1):51–54. https://doi.org/10.1093/rheumatology/keh426]
30. Rudwaleit M, van der Heijde D, Landewé R et al (2009) The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 68(6):777–783. https://doi.org/10.1136/ard.2009.108233
31. Rudwaleit M, van der Heijde D, Landewé R et al (2011) The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 70(1):25–31. https://doi.org/10.1136/ard.2010.133645
32. Garrett S, Jenkinson T, Kennedy LG et al (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 21(12):2286–2291
33. Fernández-Espartero C, de Miguel E, Loza E et al (2014) Validity of the Ankylosing Spondylitis Disease Activity Score (ASDAS) in patients with early spondyloarthritis articlefrom the Esperanza programme. Ann Rheum Dis 73(7):1350–1355. https://doi.org/10.1136/annrheumdis-2012-202976
34. Maksymowych WP, Inman RD, Salonen D et al (2005) Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum 53(4):703–709. https://doi.org/10.1002/art.21337
35. Madsen KB, Jurik AG (2010) Magnetic resonance imaging grading system for active and chronic spondylarthritis changes in the sacroiliac joint. Arthritis Care Res 62(1):11–18. https://doi.org/10.1002/acr.20008
36. Daoussis D, Liossis SNC, Solomou EE et al (2010) Evidence that Dkk-1 is dysfunctional in ankylosing spondylitis. Arthritis Rheum 62(1):150–158. https://doi.org/10.1002/art.27231
37. Akinci B, Bayraktar F, Saklamaz A et al (2007) Low transforming growth factor-β1 serum levels in idiopathic male osteoporosis. J Endocrinol Invest 30:350–355. https://doi.org/10.1007/BF03346309
38. Perpétuo IP, Caetano-Lopes J, Vieira-Sousa E et al (2017) Ankylosing spondylitis patients have impaired osteoclast gene expression in circulating osteoclast precursors. Front Med (Lausanne) 4:5. https://doi.org/10.3389/fmed.2017.00005
39. Claudepierre P, Rymer JC, Authier FJ et al (2017) A relationship between TGF-beta 1 or IL-6 plasm levels and clinical features of ankylosing spondylitis. Br J Rheumatol 36(3):400–401. https://doi.org/10.1093/rheumatology/36.3.400
40. van Lierop AH, Moester MJ, Hamdy NA, Papapoulos SE (2014) Serum Dickkopf 1 levels in sclerostin deficiency. J Clin Endocrinol Metab 99(2):E252–E256. https://doi.org/10.1210/jc.2013-3278
41. Molto A, Gossec L, Lefèvre-Colau M-M et al (2019) Evaluation of the performances of 'typical' imaging abnormalities of axial spondyloarthritis: results of the cross-sectional ILOSDESIR study. RMD Open 5(1):e000918. https://doi.org/10.1136/rmdopen-2019-000918
42. Weber U, Zubler V, Zhao Z et al (2015) Does spinal MRI add incremental diagnostic value to MRI of the sacroiliac joints alone in patients with non-radiographic axial spondyloarthritis? Ann Rheum Dis 74(6):985–992