

# Research Advances on the Mechanism and Diagnosis of Bone Bridging in Ankylosing Spondylitis

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**Abstract:** Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory disease characterized by progressive pathological new bone formation and bone bridging, ultimately leading to spinal ankylosis and functional disability. Bone bridging is a hallmark structural manifestation of AS, yet its underlying mechanisms and optimal diagnostic strategies remain incompletely understood. This review summarizes recent advances in the genetic, immunological, and molecular drivers of bone bridging in AS. We highlight HLA-B27-associated endoplasmic reticulum stress, dysregulated inflammatory cytokines (e.g. interleukin-17 and tumor necrosis factor- $\alpha$ ), and aberrant activation of osteogenic signaling pathways, including Wnt/ $\beta$ -catenin, RANK/RANKL/OPG, and bone morphogenetic protein signaling. Collectively, these interconnected processes disturb the balance between inflammation and bone remodeling, promoting ectopic ossification at enthesal and spinal sites. In parallel, we review progress in imaging-based assessment, emphasizing low-dose computed tomography, MRI-based synthetic CT, and artificial intelligence-driven radiomics for sensitive detection and quantitative evaluation of early structural changes beyond conventional radiography. Clinically, integrating mechanistic insights with advanced imaging and radiomics may enable earlier detection, risk stratification, and precision monitoring of structural progression in AS. Overall, this review provides an integrated framework to support the development of earlier diagnostic strategies and precision-targeted interventions aimed at mitigating irreversible spinal ankylosis.

**Keywords:** ankylosing spondylitis, bone bridging, HLA-B27, osteoblasts, precision medicine, radiomics, signaling pathways

## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disorder characterized by inflammatory low back pain. It primarily affects the axial skeleton, including the spine and sacroiliac joints, and significantly impairs patients' quality of life.<sup>1,2</sup> Associated manifestations may include peripheral arthritis, uveitis, and intestinal inflammation. During the initial disease phase, inflammatory pain predominates. With progressive spinal involvement, a characteristic "bamboo-like" radiographic appearance can develop, accompanied by spinal immobility, ankylosis, and deformity.<sup>3–5</sup> AS predominantly affects young males, with typical symptom onset between 20 and 40 years of age and rare initial presentation beyond 45 years. Late-onset ankylosing spondylitis (LoAS) comprises approximately 3.5%–13.8% of all cases.<sup>6,7</sup> Pain, stiffness, and restricted joint mobility substantially disrupt daily activities, while resultant deformities impose considerable socioeconomic burdens.

The pathogenesis of AS is complex and multifactorial, involving genetic predisposition (eg., the HLA-B27 allele), environmental triggers, and immune dysregulation.<sup>8,9</sup> One of the most distinctive pathological features of AS is the formation of bony bridges, characterized by excessive ossification originating from entheses—the sites where tendons and ligaments attach to bone. These osseous bridges progressively fuse adjacent vertebrae, producing the characteristic bamboo-like spine. Bone bridging contributes not only to spinal fusion and worsened pain but also to severe restriction of spinal mobility and eventual disability.<sup>10,11</sup> The mechanisms underlying bone bridging likely reflect interactions among genetic susceptibility, immune dysregulation, environmental influences, and potentially the gut microbiota.<sup>12,13</sup> Although genetic factors play a pivotal role in AS pathogenesis,<sup>14–16</sup> not all patients carry HLA-B27, indicating that other susceptibility genes may also contribute.<sup>17,18</sup>

As an autoimmune disease, AS is primarily mediated by immune dysregulation, which promotes persistent enthesitis and subsequent pathological new bone formation. Cytokines serve as pivotal mediators in this process,<sup>19,20</sup> particularly tumor

necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-17 (IL-17), which drive chronic inflammation and aberrant bone remodeling.<sup>21,22</sup> Cytokine-mediated recruitment of immune cells to inflammatory foci establishes a self-perpetuating cycle of inflammation and dysregulated tissue repair, ultimately resulting in pathological ossification. Importantly, clinical symptoms and inflammatory markers do not always parallel early structural progression, making imaging essential for detecting and monitoring bone bridging over time.

In clinical practice, conventional radiography and semi-quantitative scoring systems remain the standard for detecting and evaluating syndesmophyte formation. However, reliance on two-dimensional (2D) imaging to assess three-dimensional (3D) structures introduces limitations, including projection distortion, limited depth information, and overlapping shadows. These constraints lead to suboptimal visualization of ligamentous ossifications and limited sensitivity to structural change.<sup>23,24</sup> To address these limitations, computed tomography (CT) has been increasingly utilized for quantitative assessment of bone bridging.<sup>25</sup> CT provides comprehensive 3D information, enabling precise measurement of osteophytes along vertebral margins with high reliability and validity. CT-based assessments demonstrate superior sensitivity to change compared with the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and other radiographic scoring approaches.<sup>26</sup> Recent technological advances in low-dose CT (LDCT) have reduced radiation exposure to approximately 4 mSv while enabling high-resolution, multi-angle spinal imaging without overlapping artifacts.<sup>27,28</sup> Although LDCT delivers radiation exposure approximately tenfold lower than conventional CT, it remains roughly an order of magnitude higher than computed radiography (CR). Nevertheless, LDCT detects bone proliferation with substantially greater sensitivity, with nearly five times more new or proliferative osteophytes and bone bridges identified than with CR.<sup>29</sup> Furthermore, MRI-based synthetic CT (sCT) has been explored for assessing bone bridging and osteophytes. Current evidence indicates that sCT provides very high specificity and markedly improved sensitivity relative to conventional radiography, with diagnostic performance approaching that of LDCT.<sup>28</sup>

The primary objective of this review is to examine the mechanisms underlying pathological new bone formation in AS and to summarize advances in diagnostic approaches, thereby enhancing understanding of disease pathophysiology. By elucidating the interplay among genetic factors, immune dysregulation, and environmental influences—together with contemporary diagnostic technologies—this review aims to identify potential therapeutic targets and inform optimized clinical management strategies. A comprehensive understanding of these mechanisms and diagnostic innovations is essential for developing interventions that not only alleviate symptoms but also address fundamental disease processes, ultimately improving patient outcomes and quality of life.

Bibliometric analyses offer a useful lens for placing mechanistic and diagnostic progress in AS within the broader research landscape. A review of the 100 most-cited AS papers, for instance, points to recurring high-impact themes, with topics such as prevalence and biologic agents drawing particularly strong attention in the literature.<sup>30</sup> Read together, this type of evidence helps frame where the field has concentrated its efforts and can inform a more focused reading of current trends and near-term priorities in AS research.

## Pathophysiological Mechanisms of Bone Bridge Formation

Pathological new bone formation in AS, culminating in bone bridge development, represents a multistep cascade initiated by genetic susceptibility, driven by immune dysregulation, and executed through complex cellular and signaling pathways.

### Genetic Basis of Spondyloarthropathy

Misfolded accumulation of HLA-B27 within antigen-presenting cells triggers the unfolded protein response (UPR) and endoplasmic reticulum stress,<sup>31</sup> leading to upregulation of retinoic acid receptor- $\beta$  (RAR $\beta$ ). RAR $\beta$  enhances tissue-nonspecific alkaline phosphatase (TNAP) expression, which hydrolyzes pyrophosphate to generate inorganic phosphate, thereby promoting calcium phosphate deposition and mineralization—key steps in bone bridge formation.<sup>32,33</sup> This cascade further induces interleukin-17 (IL-17) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) secretion. These cytokines exert effects on fibroblasts at enthesal sites and bone marrow-derived mesenchymal stem cells (BM-MSCs). Fibroblasts upregulate CXCL8 to recruit immune cells, while BM-MSCs undergo directed osteogenic differentiation via CaSR-PLC $\gamma$  signaling. Collectively, these processes contribute to bone bridge development.<sup>34</sup> Additionally, HLA-B27-associated autoantibodies can directly activate osteoblasts, creating a “double hit” mechanism in which immune dysregulation synergizes with osteoclast autoreactivity to exacerbate pathological ossification.<sup>32,35,36</sup>

## Mechanisms at the Cellular and Tissue Levels

Osteoblasts serve as the primary effector cells in bone formation, undertaking the synthesis, secretion, and mineralization of the bone matrix. Their activation and proliferation, critical for new bone formation in AS, are regulated by mechanical stress, hormonal factors, and the local cytokine environment. Mechanical stimuli—including increased bone loading, obesity, and altered force transmission—prompt osteocytes embedded within the bone matrix to initiate signaling cascades that activate osteoblast, thereby commencing bone formation.<sup>37,38</sup> This mechanotransduction process involves mediators including nitric oxide and prostaglandins, which enhance osteoblast activity and extracellular matrix deposition. The Wnt/ $\beta$ -catenin pathway plays a pivotal role in regulating osteoblast proliferation and functional differentiation.<sup>39</sup> In contrast, osteoclasts mediate bone resorption, an essential process essential for physiological skeletal remodeling. These cells remove aged or damaged bone tissue, creating space for osteoblast-mediated deposition of new bone. The coordinated balance between osteoblastic bone formation and osteoclastic bone resorption is fundamental to skeletal homeostasis. Receptor activator of nuclear factor  $\kappa$ B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) jointly regulate monocyte differentiation into osteoclasts.<sup>40,41</sup> RANKL, secreted by osteoblasts and osteocytes, binds to the RANK receptor expressed on osteoclast precursors, driving their terminal differentiation and maturation. Enhanced osteoclast activity increases bone resorption, temporarily compromising structural integrity while simultaneously establishing resorption niches. These microenvironments promote osteoblast recruitment and bone deposition—ultimately contributing to pathological bone bridge formation.<sup>42</sup> Bone marrow mesenchymal stem cells (BMSCs), as multipotent progenitors, can differentiate into osteoblasts, chondrocytes, and adipocytes.<sup>43,44</sup> Their osteogenic differentiation potential is instrumental in skeletal repair and remodeling processes. Intercellular communication among BMSCs, osteoblasts, and osteoclasts maintains osseous homeostasis: osteoblasts release growth factors stimulating BMSC proliferation and osteogenic commitment, while osteoclasts generate a microenvironment conducive to BMSC survival and osteogenic commitment.<sup>44,45</sup> The cyclical interplay between bone destruction and repair during chronic inflammatory drives the progressive bone bridge formation in AS.

## Interactions Between Cytokines and Immune Cells

Cytokines serve as pivotal mediators of inflammation and pathological ossification in AS. A genome-wide association study integrating 41 inflammatory factors delineated four principal categories: pro-inflammatory cytokines (eg., IL-6, IL-17), anti-inflammatory cytokines (eg., IL-4, IL-10), chemokines (eg., MCP-1, SDF-1 $\alpha$ ), and growth factors (eg.,  $\beta$ NGF, VEGF). Notably, 9.8% of these factors—such as  $\beta$ NGF, TRAIL, and IL-1 $\beta$  (with inverse correlation of PDGF-BB)—showed significant causal associations with AS.<sup>19</sup> IL-17, predominantly secreted by Th17 cells, potentiates inflammatory responses and stimulates osteoblasts and synovial fibroblasts to express RANKL, thereby enhancing osteoclast differentiation.<sup>46</sup> This leads to early-stage bone erosion and loss, while sustained IL-17 activity—amplified by TNF- $\alpha$  and mechanical stress—establishes an inflammation–bone remodeling axis.<sup>47</sup> Clinical evidence suggests that IL-17 inhibitors (eg., secukinumab) more effectively suppress neophyte and syndesmophyte formation than TNF- $\alpha$  inhibitors, underscoring the robust association between elevated IL-17 levels and syndesmophyte progression.<sup>48,49</sup> TNF- $\alpha$ , primarily secreted by macrophages and activated T cells, represents another central cytokine initiating inflammatory cascades. Through activation of the NF- $\kappa$ B pathway and inducing of RANKL expression, TNF- $\alpha$  promotes osteoclastogenesis, resulting in vertebral margin erosion and bone loss. During prolonged inflammation and subsequent repair phase, this process may facilitate ectopic ossification, ultimately leading to bone bridging.<sup>50</sup> At spinal entheses, TNF- $\alpha$  acts synergistically with mechanical stress to enhance IL-17 secretion, thereby amplifying local inflammation and exerting a dual influence on ossification.<sup>51</sup> Fibroblast growth factors (FGFs) constitute a multifunctional family regulating cell proliferation, differentiation, and metabolic processes, with critical roles in bone remodeling. In AS, elevated FGF-23 levels correlate with chronic inflammation, hypophosphatemia, and altered bone density, collectively promoting inflammatory repair and new bone formation.<sup>52</sup> FGF-23 serves as a molecular link within the inflammation–metabolism axis that governs syndesmophyte formation, particularly at vertebral margins exhibiting fatty degeneration. By activating bone morphogenetic protein (BMP) and Wnt signaling pathways, FGF-23 drives mesenchymal stem cell differentiation into osteoblasts, facilitating syndesmophyte and subsequent bone bridge formation.<sup>53</sup>

## Signaling Pathways of Abnormal Bone Formation

Aberrant activation of specific signaling pathways contributes to the pathogenesis of AS and the development of bone bridges. The most extensively implicated pathways include the canonical Wnt/ $\beta$ -catenin, RANK/RANKL/OPG, and bone morphogenetic protein (BMP) pathways. The Wnt/ $\beta$ -catenin pathway regulates both inflammation and bone metabolism. Its dysregulated activation in AS upregulates osteogenic markers and promotes mesenchymal stem cell differentiation into osteoblasts, leading to ectopic bone formation and spinal fusion.<sup>54</sup> Molecular crosstalk between the Wnt/ $\beta$ -catenin and RANK/RANKL/OPG pathways further amplifies osteogenic activity.<sup>55</sup> Pharmacological inhibition of  $\beta$ -catenin phosphorylation has been shown to suppress fibroblast ossification, underscoring the critical role of this pathway in bone bridge formation.<sup>56</sup> The RANK/RANKL/OPG signaling axis is central to bone remodeling and inflammatory processes at entheses sites. RANKL, produced by osteoblasts and other cell types, binds to RANK on osteoclast precursors, promoting their maturation and bone resorptive activity.<sup>57,58</sup> In AS, dysregulation of this pathway—frequently characterized by an elevated RANKL/OPG ratio—enhances osteoclastogenesis and bone erosion. Pro-inflammatory cytokines further stimulate RANKL production, exacerbating osteoclast activation and contributing to the paradoxical coexistence of bone destruction and new bone formation characteristic of AS<sup>59</sup> (Table 1).

## Interactive Network of Bone Bridging Mechanisms

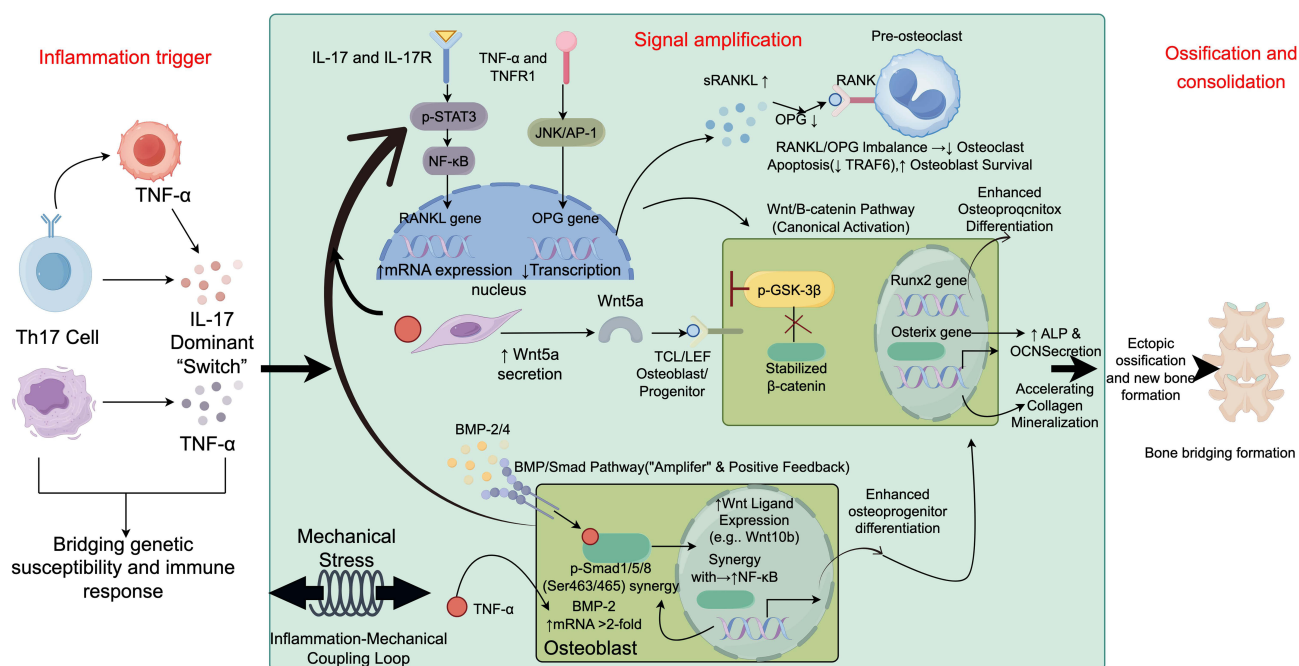
The pathogenesis of ankylosing spondylitis (AS)-associated bone bridging does not involve the isolated action of a single pathway; instead, it manifests as a highly integrated dynamic network in which inflammatory cytokines and signaling pathways interact synergistically. Inflammatory cytokines, such as IL-17 and TNF- $\alpha$ , serve as upstream “bridging agents,” linking genetic susceptibility to downstream osteogenic pathways via transcriptional regulation and signaling cascades (Figure 1). At the core of this network is the synergistic activation of the Wnt/ $\beta$ -catenin, RANK/RANKL/OPG, and BMP/Smad pathways, which form a multi-level feedback loop spanning inflammatory microenvironment remodeling to ectopic ossification.

Regulation of the RANK/RANKL/OPG axis by inflammatory cytokines constitutes the network’s initial trigger: IL-17 activates the transcription factor NF- $\kappa$ B via STAT3 phosphorylation (at Ser727), thereby inducing RANKL mRNA upregulation in osteoblasts and periosteal fibroblasts while suppressing OPG transcription. This results in an imbalance in the RANKL/OPG ratio.<sup>60,61</sup> This imbalance disrupts bone remodeling homeostasis by promoting osteoclast apoptosis (via TRAF6 signaling downregulation) and osteoblast survival, thereby indirectly amplifying downstream osteogenic signaling. Furthermore, TNF- $\alpha$  synergistically enhances this effect in concert with IL-17 by binding to the TNFR1 receptor and activating the JNK/AP-1 pathway, which in turn transcribes and activates the RANKL promoter region, thereby facilitating the transition from early inflammation to coupled bone resorption and formation.<sup>62</sup>

**Table 1** Roles of Major Signaling Pathways in Bone Bridge Formation in Ankylosing Spondylitis

Signaling Pathway	Main Components	Mechanism in AS Bone Formation	Representative References
Wnt/ $\beta$ -catenin	Wnt ligands, $\beta$ -catenin, DKK-1	Dysregulated activation enhances osteoblast proliferation and differentiation; promotes ectopic new bone formation and spinal fusion	[39,54,56]
RANK/RANKL/OPG	RANKL, RANK, OPG	Controls osteoclast differentiation and bone resorption; elevated RANKL/OPG ratio enhances erosion followed by compensatory ossification	[40,41,57]
BMP pathway	BMP-2, BMP-7, Smad proteins	Promotes osteogenic gene expression, mesenchymal stem cell differentiation, and syndesmophyte development	[52]
CaSR-PLC $\gamma$	CaSR, PLC $\gamma$ , BM-MSCs	CaSR overactivation drives BM-MSCs toward osteogenic differentiation and increases mineralization activity	[34]
FGF signaling	FGF-23, FGFR1	Links inflammation and altered bone metabolism; stimulates osteogenesis via BMP and Wnt pathways	[51,52]

**Abbreviations:** BMP, bone morphogenetic protein; CaSR, calcium-sensing receptor; PLC $\gamma$ , phospholipase C gamma; BM-MSCs, bone marrow–derived mesenchymal stem cells; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; TNAP, tissue-nonspecific alkaline phosphatase.



**Figure 1** Integrated inflammatory–osteogenic signaling network underlying bone bridge formation in ankylosing spondylitis. Genetic susceptibility and immune dysregulation initiate a pro-inflammatory microenvironment dominated by interleukin-17 (IL-17) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which act as upstream triggers linking inflammation to pathological new bone formation. These cytokines disrupt bone remodeling homeostasis by modulating the RANK/RANKL/OPG axis and promoting uncoupled bone resorption and formation. In parallel, inflammatory signaling activates osteogenic pathways, including Wnt signaling–mediated stabilization of  $\beta$ -catenin and BMP/Smad–dependent positive feedback, thereby enhancing osteoprogenitor differentiation and matrix mineralization. Mechanical stress further amplifies this inflammation–ossification coupling, ultimately driving ectopic ossification and progressive bone bridge formation at enthesal and spinal sites. Figure created with FigDraw (authorization code: OIIRT80fce).

**Abbreviations:** ALP, alkaline phosphatase; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; IL-17, interleukin-17; JNK, c-Jun N-terminal kinase; NF- $\kappa$ B, nuclear factor kappa B; OCN, osteocalcin; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor  $\kappa$ B; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; ROR2, receptor tyrosine kinase-like orphan receptor 2; RUNX2, runt-related transcription factor 2; Smad, small mothers against decapentaplegic; STAT3, signal transducer and activator of transcription 3; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

At the level of the Wnt/ $\beta$ -catenin pathway, inflammatory mediators drive its canonical activation: IL-17/TNF- $\alpha$  complex stimulation induces increased Wnt5a ligand secretion from periosteal progenitor cells. The ROR2-mediated non-canonical Wnt signaling inhibits GSK-3 $\beta$  phosphorylation (at Ser9), stabilizes  $\beta$ -catenin, and promotes its nuclear translocation.  $\beta$ -catenin then binds to the TCF/LEF complex, upregulating Runx2 and Osterix transcription. This, in turn, enhances alkaline phosphatase (ALP) and osteocalcin (OCN) secretion, thereby accelerating collagen mineralization.<sup>63</sup>

The BMP/Smad pathway functions as an “amplifier” within the network, establishing a positive feedback loop with the Wnt/ $\beta$ -catenin and RANK/RANKL/OPG axes: BMP-2/4 binds to BMPR1/2 receptors, inducing phosphorylation of the Smad1/5/8 complex (at Ser463/465). Following nuclear translocation, the phosphorylated Smad complex upregulates Wnt ligand expression (eg., Wnt10b) and synergistically activates NF- $\kappa$ B in conjunction with RANKL, thereby further enhancing osteoprogenitor cell differentiation.<sup>60,64</sup> Concurrently, TNF- $\alpha$  directly stimulates osteoblasts to secrete BMP-2, with mRNA upregulation exceeding 2-fold. Under environmental factors such as mechanical stress, this establishes an inflammation-mechanical coupling loop.<sup>60</sup> As disease progression ensues over time, a cascade unfolds: inflammation trigger  $\rightarrow$  signal amplification  $\rightarrow$  ossification consolidation. The IL-17 axis serves as the dominant “switch,” bridging Th17 immune responses to new bone formation and syndesmophyte development.<sup>65</sup>

Figure 1 summarizes these interactions and illustrates bone bridge formation as a time-evolving, integrated process. Early events are driven largely by IL-17/TNF- $\alpha$ –dominated inflammation, which then gives way to osteogenic programs—most notably BMP/Smad and Wnt/ $\beta$ -catenin signaling—that help consolidate ectopic ossification. The following section turns to multimodal imaging and considers how these changes can be captured and quantified over space and time, with an eye toward earlier detection and intervention.

## Imaging Advances in Diagnosing Bone Bridging

The intricate complex molecular and cellular mechanisms previously delineated transcend mere theoretical constructs; they leave detectable “imprints” within patients that can be captured through advanced imaging technologies. Imaging assumes a pivotal role in evaluating bone bridge formation, disease progression, and therapeutic efficacy. Continuous technological innovation has propelled imaging techniques beyond rudimentary morphological assessments towards sophisticated quantitative, functional, and predictive analyses. Recent years have witnessed the optimization of established modalities—such as X-ray, computed tomography (CT), and magnetic resonance imaging (MRI)—combined with emerging technologies including radiomics, machine learning (ML), and artificial intelligence (AI), has significantly enhanced diagnostic precision and facilitated early disease intervention (Table 2).

### Radiographic Diagnosis of Bone Bridges

Radiography constitutes the most widely utilized imaging modality for AS, primarily assessing bone bridges and vertebral fusion through semi-quantitative scoring systems such as the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).<sup>74,77</sup> However, conventional radiography is limited by subjective interpretation, low resolution, and obscuration caused by overlapping anatomical structures, which may impede the clear visualization of bone bridges. Recent advancements have introduced deep learning–based models to automate scoring processes and improve objectivity. Yen-Ju Chen et al applied deep learning algorithms to X-ray images from 554 AS patients, achieving high diagnostic accuracy in evaluating radiographic structural damage.<sup>78</sup> The integration of deep learning with traditional X-ray imaging minimizes inter-observer variability and provides a reliable tool for longitudinal monitoring of bone bridge progression.

### CT Diagnosis of Bone Bridges

Computed tomography (CT) enables high-resolution, three-dimensional visualization and has been extensively applied in clinical trials to evaluate imaging characteristics of axial spondyloarthritis (axSpA), demonstrating superior capability in detecting vertebral fusion. Owing to the high radiation dose associated with conventional whole-body CT, LDCT has become the preferred alternative. LDCT surpasses X-rays in quantifying syndesmophyte volume and height while significantly reducing radiation dose. The CT Syndesmophyte Score (CTSS), a recently developed scoring system, has been validated as a reliable quantitative tool for evaluating structural spinal damage in AS.<sup>27</sup> Nonetheless, its complexity may contribute to inter-observer variability. To address this limitation, a simplified CTSS (sCTSS) has been proposed, which maintains high reliability while reducing scoring complexity and achieves comparable sensitivity in detecting new

**Table 2** Comparison of Imaging Modalities for Detecting Bone Bridges in Ankylosing Spondylitis

Imaging Modality	Main Features	Advantages	Limitations	References
Radiography (X-ray)	2D imaging, semi-quantitative scoring (mSASSS)	Widely available; low cost	Low sensitivity; projection distortion	[23,24]
Low-Dose CT (LDCT)	3D high-resolution imaging	High accuracy for bone bridges; reduced radiation dose	Still higher dose than X-ray	[26–28]
MRI	Soft-tissue and inflammatory lesion visualization	Detects early inflammation; predicts syndesmophyte formation	Limited bone detail; expensive	[66–70]
Synthetic CT (sCT)	MRI-based computed imaging	Combines MRI safety with CT precision	Experimental; limited validation	[28]
Shear Wave Elastography (SWE)	Ultrasound-based quantitative measurement of tissue stiffness; commonly applied to assess enthesal/tendon involvement	Non-invasive; no ionizing radiation; rapid and repeatable; may detect early/subclinical biomechanical changes related to enthesitis and remodeling.	Operator- and site-dependent; limited standardization across devices/protocols; currently limited evidence for spinal assessment and for longitudinal prediction of syndesmophytes/bone bridging.	[71]
AI/Radiomics Models	Machine learning and texture analysis	Objective, quantitative, early prediction of structural damage	Requires large datasets and standardization	[67,71,74–76]

**Notes:** Radiomics refers to high-throughput extraction of quantitative imaging features used for disease characterization and prediction.

**Abbreviations:** CT, computed tomography; LDCT, low-dose computed tomography; MRI, magnetic resonance imaging; sCT, synthetic computed tomography; AI, artificial intelligence; SWE, Shear Wave Elastography.

bone formation.<sup>73,79</sup> Furthermore, computer-aided quantitative methodologies have refined syndesmophyte volume measurements, decreasing error rates from 3.01% to 1.31% and improving reproducibility across observers.<sup>66</sup> These advancements collectively establish CT—especially LDCT and automated analysis—as a robust modality for precise, reproducible assessment of bone bridging.

## MRI Diagnosis of Bone Bridges

Magnetic resonance imaging (MRI) provides superior sensitivity for detecting early inflammatory lesions and pre-radiographic bone formation, whereas X-ray and CT are more effective for evaluating established bone bridges.<sup>67</sup> MRI demonstrates clear advantages in assessing inflammation within the sacroiliac joints and spine, providing high soft-tissue contrast and enabling the early identification of non-radiographic axial spondyloarthritis (nr-axSpA).<sup>68</sup> Longitudinal studies indicate that inflammatory lesions detected by MRI at specific vertebral units correlate with a slightly increased likelihood of new ligamentous fusion at the same sites. However, inflammation alone does not fully predict the growth of existing fusions, suggesting multifactorial regulation of bone bridging.<sup>69</sup> MRI nonetheless provides quantitative assessment of inflammatory intensity and enables tracking of disease progression. Additionally, MRI frequently detects focal fat lesions at vertebral corners in AS patients. These lesions have been identified as predictive biomarkers of future bone bridge formation, with robust correlation observed between fat deposition and ensuing ossification, thereby reinforcing the prognostic utility of MRI.<sup>70</sup> To further enhance diagnostic precision, recent studies have integrated machine learning (ML) and convolutional neural networks (CNNs) with MRI analysis. The ASNET model, developed using three pre-trained CNN architectures—DenseNet201, ResNet50, and ShuffleNet—demonstrated improved diagnostic accuracy for early AS. By integrating multi-sequence MRI data, ASNET enables automated detection of early structural changes without requiring contrast-enhanced imaging, thus reducing both diagnostic costs and patient burden.<sup>72</sup>

## Shear Wave Elastography (SWE) in AS

Quantitative ultrasound has begun to attract interest in AS as a supplement to CT and MRI. Shear wave elastography (SWE) provides a noninvasive, quantitative readout of tissue stiffness and has been used to assess enthesal involvement. In a case-control study, Atik et al reported higher Achilles tendon stiffness in patients with AS than in controls, consistent with subclinical structural change at the enthesis.<sup>71</sup> On that basis, elastography-derived stiffness may reflect early biomechanical shifts along the inflammation-ossification continuum and could add value when conventional imaging is inconclusive, particularly for identifying individuals who may be prone to later osteophyte development and bridging. Evidence is still sparse, so multicenter work will be needed to harmonize acquisition protocols, define optimal anatomical targets, and test whether SWE measures carry longitudinal prognostic information.

## Advances in Radiomics Diagnosis

Radiomics represents a transformative shift from qualitative to quantitative, data-driven imaging analysis. This methodology extracts high-dimensional quantitative features—such as texture, shape, intensity, and volume—from conventional imaging modalities (X-ray, CT, or MRI) to classify lesions, assess structural damage, and predict bone bridge formation.<sup>75</sup> A standardized radiomics workflow encompasses four sequential stages: image segmentation, feature extraction, model construction, and validation. Using software tools such as PyRadiomics, hundreds of features can be extracted from regions of interest (ROIs). Subsequently, these features undergo rigorous filtering and are integrated into predictive models employing machine learning algorithms. Although radiomics applications in AS remain in their early stages, emerging evidence highlights its diagnostic potential. For instance, texture analysis of short tau inversion recovery (STIR) sequences has been employed to predict bone marrow edema activity, providing quantitative characterization of early AS inflammation. Key features, such as the gray-level co-occurrence matrix (GLCM), facilitate objective quantification of inflammatory intensity and disease activity.<sup>76</sup> Despite these advances, widespread clinical adoption remains hindered by several critical challenges. Studies have highlighted substantial variability across scanners and sites in multicenter cohorts, which introduces bias in feature extraction and compromises model performance.<sup>72</sup> Consequently, data standardization for AI-integrated radiomics is paramount to mitigate these issues. Model interpretability—the so-called “black-box” problem—also constitutes a major barrier to its adoption. Although explainable AI techniques, such as SHAP values, can attribute predictions to specific

radiomic features (eg., texture heterogeneity), clinicians often exhibit reluctance toward opaque outputs that lack transparent reasoning.<sup>80</sup> Current research predominantly relies on training small datasets (typically  $n < 500$ ), which limits generalizability in external validation studies.<sup>72</sup> However, radiomics confronts several technical and methodological challenges, including feature standardization, reproducibility across imaging platforms, and limited multicenter validation. Future research should emphasize large-sample, multicenter investigations to improve model generalizability and clinical applicability. Standardized protocols and hybrid human-AI systems can address these challenges, thereby enhancing the clinical utility of radiomics and enabling precision interventions for AS bone bridge diagnosis and management. Collectively, radiomics and AI-driven imaging signify a paradigm shift in AS diagnosis—from experience-based interpretation to data-driven precision assessment—bridging the gap between multimodal imaging data and clinical decision-making, and paving the way for personalized management strategies for AS.

## Therapeutic Challenges in Bone Bridge Formation and Multimodal Integration

Current treatment for AS primarily depends on biologic agents targeting the inflammatory axis. Agents such as the IL-17 inhibitor secukinumab and the TNF- $\alpha$  antagonist adalimumab significantly alleviate symptoms and delay bone bridge progression.<sup>81,82</sup> These agents block the Th17-IL-17 cascade and inhibit upstream inflammatory signals (eg., NF- $\kappa$ B activation), thereby mitigating the osteoblastic bias induced by RANKL/OPG imbalance.<sup>46</sup> However, ectopic ossification after bone bridge formation is inherently irreversible, underscoring a critical therapeutic bottleneck: although early intervention can reduce new bone formation by 20–40%,<sup>83</sup> late-stage patients experience resistance rates of 30–50%. Mechanistically, this arises from the independent activation of the Wnt/ $\beta$ -catenin and BMP/Smad pathways, which are unaffected by single-target inflammatory inhibition.<sup>47,63</sup> Furthermore, the lack of longitudinal monitoring along the inflammation-to-ossification timeline precludes precise identification of the intervention window in high-risk patients (eg., those with MRI-detected fatty lesions).<sup>68</sup>

To address these challenges, multimodal integration is essential: combining diagnostic imaging (eg., quantitative CTSS scoring via low-dose CT<sup>58</sup>) with mechanistic biomarkers (eg., serum IL-17 levels) to develop predictive models that guide personalized treatment strategies (eg., combining anti-TNF agents with Wnt inhibitors). This strategy not only bridges the translational gap between mechanistic insights and clinical application but also facilitates efficacy assessment via AI-assisted optimization, thereby propelling advances from mere delay to potential reversal of bone bridging. Subsequent sections will further delineate potential frameworks for such integration.

## Discussion and Outlook

The formation of bone bridges in AS is a pathological process shaped by genetic predisposition, steered by complex immune-inflammatory networks, and carried out via osteogenic cellular signaling pathways. Substantial evidence has accumulated over time, yet our current grasp of the mechanisms remains fragmented. Integrated models linking the genetic-immune axis—for instance the UPR stress tied to HLA-B27—with downstream signaling such as Wnt/RANKL crosstalk are notably absent. Diagnostic technologies including AI and radiomics have advanced quickly in recent years without fully tracing the mechanistic timeline from early inflammation visible as fatty lesions on MRI to the later development of ossification, leaving a clear gap in predictive capability.

Biologic therapies can slow structural progression, yet heterogeneous responses and treatment resistance remain common in clinical practice. Several mechanistic gaps still limit progress. Longitudinal GWAS and Mendelian randomization studies are relatively scarce, which makes it difficult to dissect time-dependent gene-environment effects on bone bridging—microbiome-mediated modulation of HLA-B27 is one plausible example. Single-cell RNA sequencing data are also limited, leaving the spatiotemporal heterogeneity of Th17 populations and osteogenic progenitors only partially resolved. Similar constraints appear in radiomics and AI research: many studies rely on small, single-center datasets with modest external validation, increasing the risk of overfitting and weakening generalizability; widely adopted, standardized datasets remain uncommon.

Beyond algorithmic performance, the safety of AI use in AS also depends on the reliability, information quality, and readability of what these systems produce. Kara et al compared responses to commonly asked AS-related questions across three popular chatbots (ChatGPT, Gemini, and Perplexity), scoring outputs with established readability indices (eg., Flesch Reading Ease, SMOG, Gunning Fog) and quality/reliability tools (EQIP, GQS, modified DISCERN, and

JAMA benchmarks). In their analysis, readability often failed to meet recommended targets, and quality and reliability differed across platforms, which raises practical concerns about consistency for end users.<sup>84</sup> Chatbot answers are not the same as imaging-based radiomics outputs, but the message carries over. AI tools intended to support AS care should be built and reported with transparent data provenance, standardized evaluation, and external validation, with clinician oversight where decisions or counseling are involved. When outputs are patient-facing, readability is not a cosmetic issue; it shapes comprehension and, ultimately, safe use in real-world settings.

An “inflammation–ossification digital twin” could be a useful long-term framework for AS, especially if it links single-cell atlases with multimodal imaging and genetic information. At present, it is best viewed as a hypothesis-generating idea rather than a ready-to-deploy solution; prospective, multicenter studies with standardized longitudinal imaging and biomarker sampling would be needed to test it rigorously. On the mechanistic side, CRISPR-based screens could help confirm key regulatory nodes—IL-17–Wnt crosstalk is one plausible target—and, in time, inform individualized risk stratification. Clinically, the immediate priorities are more practical: improve cross-center data sharing, make models easier to interpret, and define earlier intervention windows aimed at preventing or at least slowing structural progression. Remodeling of established bone bridges remains speculative and should be presented cautiously until stronger evidence emerges.

## Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Ethical Approval

This article is a narrative review and does not involve any new studies with human or animal subjects performed by any of the authors.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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