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Dickkopf-1 in rheumatoid arthritis: Mechanistic insights, imaging associations, and emerging therapeutic strategies

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Abstract

Rheumatoid arthritis (RA) is a persistent autoimmune disease which is synovial inflammation, progressive joint destruction, and functional disability. A soluble canonical Wnt/β-catenin pathway inhibitor called dickkopf-1 (DKK-1) has become a key regulator of pathological bone remodelling in RA. DKK-1 dissociates bone formation with resorption by opposing Wnt signaling by degrading lipoprotein receptor-related protein 5/6, inhibiting osteoblastogenesis, reducing osteoprotegerin expression, and increasing osteoclastogenesis mediated by RANKL, thus promoting joint erosion and structural erosion. A systematic literature review of preclinical and clinical papers was conducted in order to evaluate the DKK-1 molecular pathogenesis of RA. Synthesis of evidence was conducted in the area of DKK-1 associations with inflammatory (C-reactive protein, erythrocyte sedimentation rate) and autoantibodies (rheumatoid factor, anti-citrullinated protein antibodies), disease activity (disease activity score 28) and radiographic erosion (index) measures. The modulatory role was examined by looking at genetic polymorphisms (rs1896367, rs1896368). Imaging modalities such as power Doppler ultrasound, radiography and magnetic resonance imaging were evaluated on their complementary relation with DKK-1 levels. The therapeutic approaches to DKK-1, such as preclinical blockade models and indirect control with tumor necrosis factor-alpha inhibitors were critically analyzed. High serum and synovial DKK-1 levels were significantly associated with inflammatory indices, autoantibody titers, activity of the disease and structural damage on imaging. The polymorphism at the rs1896367 locus predisposed the patients to aggressive erosive disease, and the polymorphism at the rs1896368 provided some protection. Multimodal imaging showed complementary correlations, which made DKK-1 an ideal early detection and treatment-monitoring biomarker. Preclinical DKK-1 blockade reverted erosive phenotypes, stimulated osteoblast activity and prevented the erosion development, although the inflammation persisted. Tumor necrosis factor-alpha blockers indirectly suppressed DKK-1, confirming that it is a useful pharmacodynamic marker. DKK-1 is a multidimensional biomarker that combines molecular genetics, immunopathology and imaging in RA. Although promising as a therapy, DKK-1 as a precision

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rheumatology target needs to overcome various translational challenges, such as ectopic ossification, risk of joint fusion, variability of assays, lack of standardized thresholds, and large-scale clinical trials. The research and existing trials show considerable heterogeneity through their assay platforms not being standardised, difference in reporting units for DKK-1 concentrations, The biomarkers like RANKL and osteoprotegerin are sensitive to storage, the disease stage and duration also affect the DKK-1 concentrations as it is higher in early RA, Patients under treatment also report significantly reduced DKK-1 levels, genetic variations, Higher concentration in synovial compartment, faster clearance from serum than synovium. The DKK-1, however promising as a marker of early RA, poses numerous challenges as mentioned above before being brought into everyday use. There may be future studies on its safety, standardisation, and concentration among the human population. In India, it is still a novelty that has not yet been made into large-scale clinical trials, so that future research could push forward this biomarker towards clinical trials.

Key Words: Dickkopf-1; Rheumatoid arthritis; Wnt/β-catenin; Osteoprotegerin; RANKL; Osteoclastogenesis

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Core Tip: Dickkopf-1 (DKK-1) is a key regulator of bone remodeling in rheumatoid arthritis, driving erosion by inhibiting Wnt signaling, suppressing osteoblasts, and enhancing RANKL-mediated osteoclastogenesis. Elevated DKK-1 correlates with inflammation, autoantibodies, disease activity, and imaging indices, while genetic variants modulate risk. Though blockade shows therapeutic promise, safety concerns and assay variability remain. DKK-1 offers a multidimensional biomarker

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for prognosis, monitoring, and precision-targeted therapy in rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a persistent autoimmune disease that manifests itself in the peripheral polyarthritis of the synovial joints, resulting in the destruction of the joints to the extent of deformity. It is prevalent in almost 0.5%-1% of the world's adult population, with women and the elderly being more affected[1,2].

An imbalance between bone-forming and bone-resorbing activity within inflamed joints is the causative in RA. Dickkopf-1 (DKK-1) is a soluble endogenous inhibitor of the canonical Wnt/β-catenin signaling pathway and was found to be a molecular mediator of such an imbalance[3]. DKK-1 induces the erosion that characterizes active RA by inhibiting osteoblast differentiation and indirectly promoting the activity of osteoclasts[1,4-7].

DKK-1 levels in serum and synovial fluid have been explored as a diagnostic/prognostic biomarker and a potential therapeutic target of RA. There is evidence that DKK-1 levels are aligned with disease activity, severity of synovitis, and radiographic progression[2,8-10]. Diversity in assay platforms, overlap with other inflammatory diseases in elevating DKK-1, and lack of standard cutoff values have restricted its use in normal clinical practice[11,12].

This narrative review summarizes and critically evaluates the literature that exists on DKK-1 in RA primarily in terms of its biological activity, relationship with disease activity and structural outcomes, its possible use in the diagnosis and prognosis of the condition, and the limitations that need to be overcome before it can be clinically used. Combining the results of research, we are assessing the possibility of using DKK-1 as a trustworthy biomarker and commenting on the future perspectives of research and treatment creation. This review highlights the progression of disease with the use of DKK-1 and the imaging modalities. The review also deals with the effectiveness of DKK-1 levels being used as a biomarker. We have also brought out the preclinical studies that, despite showing the effectiveness of DKK-1, also show the safety considerations of pathologic bone fusion and possible cancer development.

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METHODOLOGY

The review aimed to approach the novelty known as DKK-1 through its biology, pathophysiology, polymorphisms, its use as a marker in RA, correlation with disease activity through predicting radiographic progression and treatment response as a pharmacodynamic marker and the limitations and safety considerations. The relevant literature was selected across PubMed, Scopus, Web of Science, and EMBASE. After the selection of literature, they were exported to a reference management software. Relevant studies were identified against the inclusion criteria.

Inclusion criteria

Systematic and narrative reviews, clinical and preclinical trials and animal studies about DKK-1 in Orthopaedics. The article must have been published within the past 25 years. The population included normal test humans and humans with RA. The studies focus on the effectiveness of DKK-1 as a Biomarker. The search was done on PubMed, Google Scholar, and Scopus. The keywords were – dickkopf-1, serum DKK-1 levels, rheumatoid arthritis, genetic variation of DKK-1, biomarkers in RA, imaging in RA.

To synthesis the data in this review under the headings biology, pathophysiology, polymorphisms, its use as a marker in RA, correlation with disease activity through predicting radiographic progression and treatment response as a pharmacodynamic marker and the limitations and safety consideration a narrative type of approach was used. The comparison between the imaging modalities and DKK-1 was tabulated, and the correlation between DKK-1 and other inflammatory factors was also studied.

WNT/B-CATENIN SIGNALING IN BONE HOMEOSTASIS

The canonical Wnt/β-catenin signaling pathway is a regulator of skeletal development and bone homeostasis[13,14]. The Wnt ligand's functions include stimulation of osteoblastogenesis, enhancement of bone matrix production, and

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inhibition of osteoclast-mediated bone resorption[15-18].

Pathway activation

When the Wnt signaling pathway is in an active state, the ligands that belong to the pathway bind to Frizzled receptors and co-receptors low-density lipoprotein receptor-related protein 5/6 (LRP5/6)[19,20]. This double binding of ligands leads to the recruitment of a scaffold protein called Dishevelled and triggers the phosphorylation of the LRP5/6 cytoplasmic tail[21]. The phosphorylation reaction inactivates β-catenin complex that was produced for the destruction of the bone matrix. The complex consists of Axin, APC, and GSK-3b[15,19,22,23]. With the destruction complex inhibited, the newly synthesized β-catenin accumulates in the cytoplasm and is translocated to the nucleus, where it binds with TCF/LEF transcription factors and activates the Wnt target genes. Among these target genes, c-MYC and cyclin D1 promote osteoblast proliferation, differentiation, and bone matrix deposition[24-28].

When the Wnt signaling pathway is in an inactive state, the destruction complex remains active, therefore leading to GSK-3 and CK1 subsequently phosphorylating β-catenin, leading to ubiquitination and proteasomal degradation[4,29]. The net result is reduced nuclear β-catenin and reduced transcription of anabolic genes in the bone[15,28].

Wnt-mediated anti-osteoclastic effects

Along with direct anabolic effects on osteoblasts, the canonical Wnt signaling shows an important anti-resorptive action through its modulation of the RANK-RANKL-osteoprotegerin (OPG) axis[25,26]. The Wnt signaling in mature osteoblast cells induces the synthesis of OPG, which acts as a decoy receptor for RANKL[25,26,30]. By binding to RANKL, the OPG prevents RANKL from engaging with RANK on osteoclast precursors, therefore suppressing the osteoclast differentiation and bone resorption[31,32]. This is a crucial link between the anabolic and anti-resorptive functions of bone metabolism, and its imbalance is the main cause of the impairment of joints in RA[29,33].

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PATHOPHYSIOLOGY OF DKK-1 IN RA

DKK-1 is an endogenous and soluble Wnt inhibitor that causes an imbalance in the Wnt signaling at the level of LRP5/6 co-receptors[34]. It binds with high affinity to LRP5/6, which progressively leads to them being internalised and degraded. This prevents the formation of functional Wnt-Frizzled-LRP5/6 signaling complexes, therefore effectively stopping the anabolic Wnt response[5]. In the case of RA, synovial fibroblasts, macrophages, and osteoblasts present within the inflamed joint may express increased levels of DKK-1 under the influence of tumor necrosis factor-alpha (TNF-α) and other pro-inflammatory cytokines, therefore reaching high local concentrations that suppress bone repair[2,35].

The downstream consequences are dual. Initially, the suppressed Wnt signaling reduces the expression of OPG in osteoblast cells[36]. This shifts the OPG: RANKL ratio toward RANKL excess, thereby increasing osteoclast recruitment, differentiation, and activity[37-39]. Next, the reduced β-catenin-dependent transcription reduces the osteoblast survival and function, making bone repair harder. Together, these mechanisms produce a state of bone remodelling where resorption is more than formation, leading to periarticular erosions in RA[29,35].

Collagen-induced arthritis (CIA) in mouse models was studied, where circulating DKK-1 levels correlated with the severity of bone disfigurement. DKK-1 was also found to increase the number of myeloid-derived suppressor cells. These cells are capable of differentiating into osteoclasts, therefore promoting bone resorption[40]. In the synovial fibroblasts from patients diagnosed with very early RA (eRA) (disease duration below 3 months), high DKK-1 levels were found to increase lymphocyte adhesion in vitro. This suggests that DKK-1 causes structural damage to begin before clinical symptoms become chronic[41,42]. The mechanism of DKK-1 in the joint milieu is depicted in Figure 1.

GENETIC POLYMORPHISMS OF DKK-1 IN RA

Genetic variants within the DKK-1 Locus modulate both the expression level of the protein and the severity of structural damage in RA. Two single-nucleotide

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polymorphisms have received particular attention: (1) Rs1896367; and (2) Rs1896368[43-45].

Rs1896367: Risk variant for structural damage

Aggressive structural damage is linked with the rs1896367 variant, especially in the feet. Carriers exhibited a higher level of bone erosion (P = 0.026), more joint space narrowing (JSN) (P = 0.005), and higher Sharp-van der Heijde Scores (SHS) (P = 0.016) than non-carriers in a Colombian cross-sectional cohort of patients with eRA[46-48]. It is worth noting that a Simple Erosion Narrowing Score (SENS) over 6 in this group had only a probability of 0.1% of occurrence by chance, meaning that there was a strong genetic-structural relationship[8,49,50]. Homozygous carriers of rs1896367 also showed an association with periodontal disease (P = 0.009), which further expanded the implications of this polymorphism to the systemic[51,52].

Rs1896368: Protective variant

On the other hand, the lower radiographic damage is linked to the variant, which is the rs1896368. Carriers exhibit lower risk of radiographic progression (P = 0.05), reduced JSN in hands and feet (P = 0.026), and no cases with SENS above 6 in available cohorts (P < 0.001)[43,46,53]. These findings collectively indicate that DKK-1 genetic variation can serve as a biological modifier of structural outcomes in RA, with clear potential relevance to patient stratification in precision medicine frameworks[43].

DKK-1 AS A BIOMARKER IN RA

Serum levels: Comparative and quantitative data

On reviewing previous literature, we came across a systematic review and meta-analysis pooling 9 studies (1305 RA patients *vs* 504 healthy controls) that has confirmed that serum DKK-1 level is elevated in RA, with a pooled standardized mean difference of 0.79[8,9]. The reported serum DKK-1 concentrations range from 66 ng/mL to 453 ng/mL in RA patients, compared with 15-87 ng/mL in healthy controls[2,8,54]. Similarly, one study found mean DKK-1 levels of 5888 ± 1868

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pg/mL in RA patients *vs* 1524 ± 430 pg/mL in controls[11]. In postmenopausal RA women, DKK-1 levels were higher than those of controls and were inversely related to bone mineral density loss, similar to a systemic skeletal disease[2,54].

CORRELATION WITH DISEASE ACTIVITY AND INFLAMMATORY MARKERS

DKK-1 demonstrates correlation with indices of disease activity and systemic inflammation. The study conducted at Zagazig University reports a very strong positive correlation with composite indices like disease activity score 28 (DAS-28), C-reactive protein (CRP), and erythrocyte sedimentation rate. The high positive value is probably due to the study being carried out only on 60 individuals with the disease. These results encourage us to be cautious and not to generalise the RA findings across populations. Another variability in correlation arises when patients at different stages of disease are exposed to the same treatment modality. Key findings from published studies are summarized in Table 1[8,9,11,42,54-61].

PREDICTIVE VALUE FOR RADIOGRAPHIC PROGRESSION

Baseline circulating DKK-1 predicted radiographic progression, specifically erosion development, in eRA patients receiving etanercept, independent of CRP and disease activity scores[2]. Furthermore, the DKK-1/R-spondin 1 (RSPO1) ratio was more strongly affiliated with erosive disease and the rate of radiographic progression than DKK-1 alone, since RSPO1 is a potent Wnt pathway agonist that functionally opposes DKK-1. This ratio method can thus be more precise in reflecting pathway-level dysregulation than either of the two molecules itself[62,63]. The levels of DKK-1 in the cross-sectional RA cohort correlated both with the erosion score and negatively with bone mineral density, which supports its dual participation in the process of periarticular bone loss and systemic bone weakening[64-67].

RESPONSE TO TREATMENT AS A PHARMACODYNAMIC MARKER

TNF-α blocker and interleukin-1 (IL-1) receptor antagonist treatment decrease serum levels of DKK-1, and these data indicate that DKK-1 is a dynamically regulated

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protein in response to anti-inflammatory therapy. Radiographic outcome has been investigated as dependent on DKK-1 changes in biological therapy, which indicates that it may serve as a pharmacodynamic biomarker of anti-erosiveness[68-70]. Notably, not all cohorts with strict therapeutic control have shown any significant changes in DKK-1 among the biologic classes, suggesting that the intensity of treatment and disease stage bring heterogeneity to the pharmacodynamic signal[53,54].

LIMITATIONS OF CURRENT BIOMARKER EVIDENCE

Heterogeneity is seen in findings across disease activity scores (DAS-28, CDAI, SDAI, RAPID3), which is a limitation that is repeatedly seen where DKK-1 is incorporated, appearing stronger in early and active RA than in long-standing disease[8,71]. The predominance of cross-sectional study designs used to study the DKK-1 levels prevents us from providing a definitive aetiology. Large-scale multicentre longitudinal studies validating DKK-1 as a predictor of future erosive damage remain limited[9,12,54].

Reported thresholds (*e.g.*, approximately 2726.97 pg/mL) show high sensitivity/specificity in isolated studies. Lack of universal validation across populations, labs, and different disease stages[11,12]. The usage of different ELISA kits with different antibodies and experimental standards gives different values. For DKK-1 concentrations, many reports use different units (pg/mL *vs* ng/mL). These factors limit cross-study comparisons[9,66,72,73].

Serum DKK-1 is not always consistent with joint-specific Wnt signaling. Local TNF-α induces the production of DKK-1 in synovial fibroblasts generates high concentrations in synovial fluid that may be independent of the circulating signal. Also, the clearance of DKK-1 from serum is faster than from synovial fluid, thus making comparisons between compartments unreliable[12,54,71,74]. *DKK-1* gene polymorphisms may alter expression, activity, or association with bone disfigurement. Biomarker performance may vary across ethnicities or genetically distinct populations[43,46].

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IMAGING CORRELATIONS AND DKK-1

Power Doppler ultrasound

The power Doppler ultrasound (PDUS) detects active synovial inflammation through neo-angiogenesis. It is related to systemic inflammation through erythrocyte sedimentation rate levels (r = 0.31, P = 0.01), CRP levels (r = 0.45, P < 0.01), and related to clinical disease activity through DAS-28 score (r = 0.30, P = 0.01)[42,75,76]. PDUS is also related to DKK-1, ultrasound erosion count, and ultrasound erosion rate. This further strengthens its relation with molecular indices[77]. It is also related to synovial histology as it correlates with CD3+ T-cell (r = 0.54) and CD20+ B-cell (r = 0.54) infiltration.

From a prognostic standpoint, PDUS can detect the early stage of disease even at clinically silent metacarpophalangeal joints. PDUS can also predict disease relapse during dose reduction or therapy discontinuation, and it tracks treatment response dynamically[72,78]. The pauci-immune histopathological pathotype is the most resistant to current treatments, and its identification by synovial biopsy combined with PDUS may be critical for therapeutic decision-making[75,79].

Synovial thickening ultrasound

The synovial thickening ultrasound is a measure of synovial hypertrophy and is analogous to the chronic nature of the disease rather than active inflammation. On comparison with inflammatory marker synovial thickening ultrasound is similar only to CRP (r = 0.33, P = 0.01)[75,78,80,81].

Conventional radiography

Radiographic assessment of RA uses digital antero-posterior views of hands and feet scored with the SHS or the SENS to quantify joint erosion (JE) and JSN[8,49,82]. DKK-1 correlates with radiographic severity as measured by SENS. Rheumatoid factor at its baseline is more related to 12-month JE score (r = 0.46, P < 0.01) and erosion progression (r = 0.43, P < 0.01)[82]. In practical DKK-1 may not predict radiographic progression if the patient is undergoing active treatment[83].

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Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the most sensitive imaging technique for eRA detection. The findings, such as synovitis, bone marrow oedema (BME), and early erosions, are visible on MRI before conventional radiographs[84-88]. BME is the best predictor of future radiographic progression it can show active osteitis and risks of structural damage. In early polyarthritis, MRI can detect synovitis in carpal joints and flexor tendon sheaths, which is the most reliable predictor of progression to classifiable RA[84,86,89]. Conversely, the absence of MRI synovitis has a high negative predictive value, assisting clinicians in excluding RA and avoiding unnecessary initiation of disease-modifying therapies[86,87]. The comparative roles of ultrasound, radiography, MRI, and DKK-1 across key clinical domains are presented in Table 2.

THERAPEUTIC RATIONALE FOR DKK-1 TARGETING

Preclinical evidence

A DKK-1 blockage is being searched in animal models like human TNF-transgenic mice, collagen-induced arthritis, and glucose-6-phosphate isomerase arthritis[90,91]. Anti-DKK-1 treatment in these models converted a bone-destructive phenotype into a bone-forming one. This proves DKK-1 is a molecular switch between the destruction and repair of bone[92].

Anti-DKK-1 treatment prevented inflammatory bone erosions even in the case of active inflammation, leading to reduced bone loss and inflammation[12,93]. Histological studies in these animal models showed increased osteoblast numbers, osteoid deposition, and osteophyte formation inside synovial joints following DKK-1 blockade. However, in the case of spinal and sacroiliac joint models, the DKK-1 inhibition produced pathological joint fusion, thus showing that excessive Wnt activation can produce ectopic ossification and ankylosis[93,94].

These preclinical trials do highlight some mechanistic uncertainties despite the promising potential. These show that there is a possibility of pathologic bone formation, including ectopic ossification and joint fusion. Another worrisome concern relates to the biological effects of Wnt pathway modulation, as it is involved

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with several oncogenic pathways. The long-term risk of cancer development due to DKK-1 inhibition is uncertain. From the perspective of clinical development, DKK-1 has yet to enter phase-III clinical trials, and the existing studies have yet to establish efficacy in larger populations.

Indirect modulation by current therapies

TNF-α is an inducer of DKK-1 production in synovial fibroblasts. Inhibition of synthesis of TNF-α with biologics such as etanercept, adalimumab, and infliximab lowers serum DKK-1 toward normal ranges, and changes in DKK-1 during treatment are known to affect the progression of disease[2,68]. IL-1 receptor antagonists (anakinra) and conventional DMARDs such as methotrexate are also known to reduce DKK-1 levels[68,70].

A contrasting observation is seen in psoriatic arthritis (PsA). In PsA, the baseline DKK-1 may be lower than that present in healthy controls and can increase after anti-IL-17A treatment. Thus DKK-1 has a disease-specific and pathway-specific behaviour that proves that DKK-1 cannot be generalized across spondyloarthropathies[16,95].

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SAFETY CONSIDERATIONS AND LIMITATIONS FOR THERAPEUTIC DEVELOPMENT

DKK-1 blockade has ample risks despite its clear therapeutic effect. Animal models demonstrate that Wnt activation from DKK-1 inhibition can lead to pathological new bone formation (ectopic ossification) and joint fusion, especially at the axial skeleton[93]. In conditions where Wnt signaling is already heightened, such as PsA or axial spondyloarthritis, DKK-1 blockade could worsen ankylosis[70,96]. Wnt signaling interacts with oncogenic pathways, and the aspect of cancer risk is not known[97].

The reaction between DKK-1, sclerostin, and RANKL is not fully understood. We are currently unclear if DKK-1 inhibition alone is enough or if blocking both DKK-1 and sclerostin might give better outcomes[98,99]. The therapeutic program has not entered clinical trials, and no phase III clinical trials of DKK-1 inhibitors in

RA are reported. Careful dose-finding, imaging-based monitoring, and patient phenotyping will be essential components of any future trials.

GAPS IN CURRENT EVIDENCE

The use of DKK-1 levels as a biomarker in RA faces several challenges that must be addressed before it comes to clinical use. Standardisation of ELISA kits and measuring units is the first challenge. Serum levels and synovial fluid levels of DKK-1 constantly differ because of local TNF-α, which induces DKK-1 production in synovial fibroblasts, and the two compartments exhibit different clearance times[9,66,99].

On the imaging side, radiological assessment uses SENS for plain radiographs, OMERACT-defined scoring for ultrasound, and RAMRIS (RA MRI score) for MRI, and the absence of a unified scoring framework reduces cross-modality comparability when correlating with DKK-1[8,12,49]. Biologically, the relationship among DKK-1, sclerostin, RSPO1, and RANKL remains incompletely mapped, and extra-articular effects of elevated or suppressed DKK-1 on trabecular bone and systemic osteoporosis require dedicated longitudinal investigation[98,99].

DKK-1 is a glycoprotein and endogenous soluble Wnt inhibitor that normally maintains the balance in bone homeostasis by reducing new bone growth. In RA, the imbalance is due to inflammatory cytokines that convert it into a driver of joint injury. The bone remodelling patterns seen in degenerative osteoarthritis (characterized by pathological new bone formation) and RA (characterized by bone resorption) can be explained by the different behaviour of DKK-1 in these two diseases[100]. Serum DKK-1 levels are higher in RA patients than in controls, with DAS-28 score reaching $r = 0.960$ in some studies and CRP reaching $r = 0.640$[8,9,11,42,54]. The genetic difference is clear, where rs1896367 was associated with more frequent erosions in the feet, higher SHS, and greater JSN, collectively identifying a subgroup at high risk for aggressive structural damage[46,101,102].

The imaging data establishes a framework for the clinical progression of disease. PDUS indicates active inflammation along with DKK-1, which can predict future structural damage through persistent synovial signals. MRI provides the highest-

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sensitivity detection of BME as it is the strongest predictor of radiographic progression of disease. Conventional radiography is insensitive for early disease but serves as a prognostic indicator through baseline erosion quantification[42,75,76,84,86].

The preclinical evidence for DKK-1 blockade has demonstrated that erosion prevention that is not dependent on inflammation suppression is achieved. The trials also offer the possibility of a bone-protective intervention that acts as complements to existing anti-inflammatory biologics[92,93,103]. The challenge lies in translating this new intervention safely, given the risks of ectopic ossification, the pathway's intersection with oncogenesis, and the absence of phase III trial data[9,43,97].

CONCLUSION

RA is a clinical spectrum of pathologies affecting the joints, ranging from mild, self-limiting disease to severe disability. Intervention at the therapeutic window is essential to prevent structural damage. DKK-1 drives JE by suppressing Wnt signaling and causing an imbalance in bone homeostasis. Genetic variants among humans have different DKK-1 production thus influencing circulating DKK-1 levels. Imaging modalities such as PDUS and MRI BME are markers of progression of disease. Integration of histology, biomarkers, genetic loci, and imaging leads to better and safer standardization of the intervention. Standardization of ELISA kits and measuring units is the first challenge. The DKK-1 inhibitors must address the risk of ectopic ossification, genetic variations and long-term safety monitoring. If these challenges are overcome in the future, then DKK-1 may evolve into both a biomarker and a therapeutic target.

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Figures and Tables

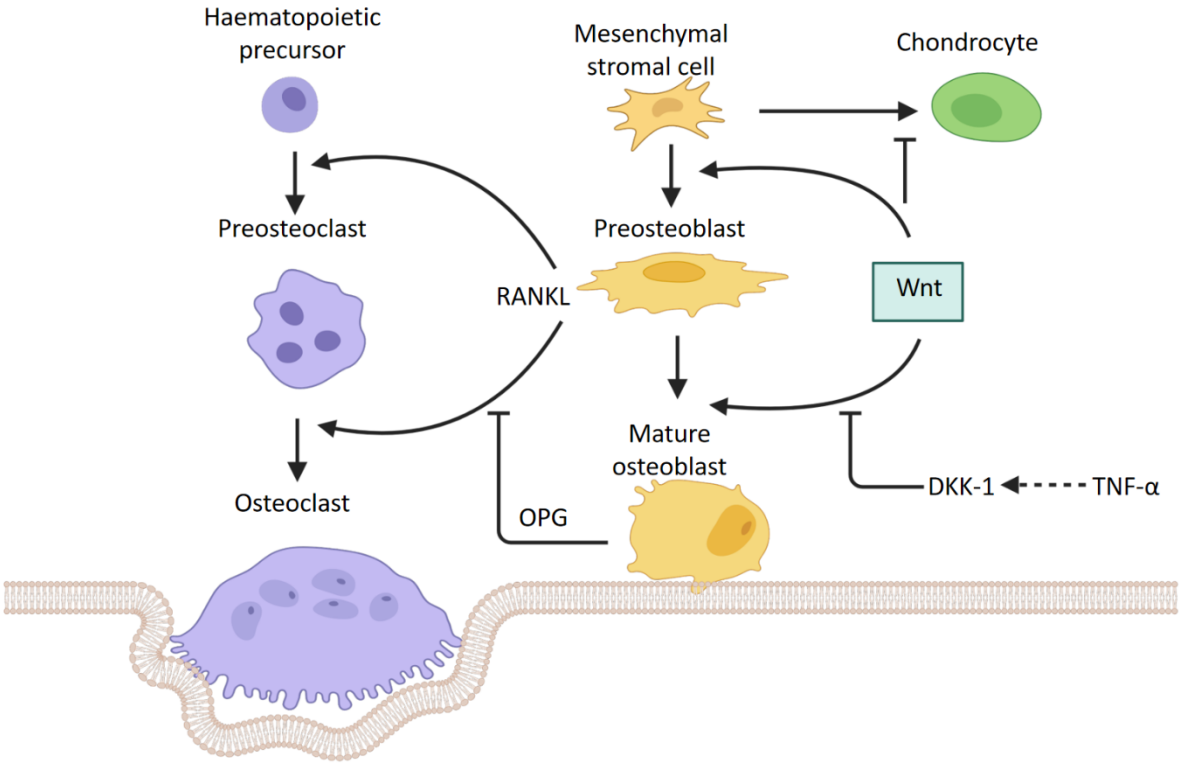


Figure 1 Mechanism of dickkopf-1 in joint milieu. Figure 1 is drawn in Biorender.com. DKK-1: Dickkopf-1; TNF-α: Tumor necrosis factor-alpha; OPG: Osteoprotegerin.

Table 1 Correlations between serum dickkopf-1 and indices of disease activity, inflammation, and autoimmunity in rheumatoid arthritis

Parameter	Correlation finding	Ref.
DKK-1 *vs* DAS-28	r = 0.960 (very strong positive)	Ali *et al*[9], Juarez *et al*[54], Fang *et al*[55]
DKK-1 *vs* DAS-28 (Spearman)	*rho* = 0.75	Abdulaziz *et al*[56], Coras *et al*[57]
DKK-1 *vs* CRP	r = 0.640 (significant positive)	Santos *et al*[11], Sadek *et al*[42], Coras *et al*[57]
DKK-1 *vs* ESR	r = 0.498 (significant positive)	Santos *et al*[11], Sadek *et al*[42], Coras *et al*[57]
DKK-1 *vs* RF	r = 0.473 (significant positive)	Ali *et al*[9], Santos *et al*[11]
DKK-1 *vs* Anti-CRP	r = 0.478 (significant positive)	Ali *et al*[9], Santos *et al*[11]

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antibodies		
DKK-1 *vs* RA	r = 0.876 (very strong positive)	Santos *et al*[11]
DKK-1 *vs* steinbrocker functional grade	Higher levels in class III (4689-8092 pg/mL)	Ma *et al*[8], Ali *et al*[9], Sadek *et al*[42], Juarez *et al*[54]
Diagnostic cut-off	2726.97 pg/mL; sensitivity of 98.18%, specificity of 100% for active RA by DAS-28	Procaccia *et al*[58], Bagherzadeh-Fard *et al*[59], McWilliams *et al*[60], Pertsinidou *et al*[61]

DAS-28: Disease activity score 28; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; RA: Rheumatoid arthritis; RF: Rheumatoid factor.

Table 2 Comparative roles of imaging modalities and dickkopf-1 in rheumatoid arthritis

Parameter	**Ultrasound**	**Radiography**	**MRI**	**DKK-1**
Detects early synovitis	Yes (PDUS best)	No	Yes	Indirectly
Detects bone marrow edema	No	No	Yes (strongest predictor)	No
Sensitivity in eRA	High	Low	Very high	Moderate-high
Predicts future damage	Yes (persistent PDUS)	Yes (if baseline erosions)	Yes (BME)	Yes (erosions, JSN)
Remission assessment	Subclinical synovitis	No role	Confirms deep remission	Ongoing bone injury risk
Correlation with DKK-1	PDUS: ESR, CRP, DKK-1	RF, ACPA, DKK-1	BME: Erosive risk markers	N/A
Treatment monitoring	Excellent	Poor	Good (costly)	Good; falls with biologics

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Key limitation	Operator dependent	Insensitive early disease	Cost and access	Assay variability

ACPA: Anti-citrullinated protein antibodies; BME: Bone marrow edema; CRP: C-reactive protein; DKK-1: Dickkopf-1; eRA: Early rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; JSN: Joint space narrowing; MRI: Magnetic resonance imaging; N/A: Not applicable; PDUS: Power Doppler ultrasound; RF: Rheumatoid factor.

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