Dickkopf-1 in Rheumatoid Arthritis: A Novel Indicator of Inflammation, Bone Destruction, and Disability

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ABSTRACT

Background:

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovitis, systemic inflammation, and progressive joint destruction, leading to functional disability and decreased quality of life. A key feature of RA is the imbalance between bone formation and resorption, primarily driven by pro-inflammatory cytokines and dysregulated signaling pathways. Among these, the Wnt/β-catenin signaling pathway plays a crucial role in bone metabolism. Dickkopf-1 (DKK-1), a secreted glycoprotein and a natural inhibitor of this pathway, has emerged as a pivotal regulator of bone remodeling. Elevated DKK-1 levels have been associated with increased osteoclast activity, suppressed osteoblast differentiation, and enhanced joint damage in RA. Consequently, DKK-1 is under investigation as a potential biomarker reflecting disease activity and functional impairment in affected individuals. This review aims to provide a comprehensive overview of the role of Dickkopf-1 in the pathogenesis of rheumatoid arthritis, with a particular focus on its utility as a biomarker for assessing disease activity and functional disability. The article highlights the biological function of DKK-1, its regulation by pro-inflammatory cytokines such as TNF-α, its impact on bone homeostasis, and its clinical associations with RA progression and severity. Moreover, parallels with other autoimmune and degenerative diseases are explored to further contextualize DKK-1's significance.

Conclusion: Emerging evidence supports the role of DKK-1 as a key mediator in RA-related joint damage and systemic bone loss. Its measurable serum levels and mechanistic involvement in both inflammation and bone remodeling suggest that DKK-1 could serve as a reliable biomarker for disease monitoring and a potential therapeutic target. Further longitudinal and interventional studies are warranted to validate its clinical application and to determine whether modulation of DKK-1 can contribute to improved outcomes in RA patients.

Keywords: Dickkopf-1, Rheumatoid Arthritis, Disability

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that primarily targets synovial joints and, in many cases, causes extra-articular and systemic complications. Affecting nearly 1% of the global population, RA leads to significant morbidity and disability, particularly in women and middle-aged individuals, although sex differences diminish with age [1]. The disease often presents as a symmetrical polyarthritis, with pain, stiffness, and swelling in the small joints of the hands and feet. Persistent inflammation contributes not only to joint destruction but also to fatigue, functional decline, and impaired quality of life [2].

The pathogenesis of RA is complex, involving genetic susceptibility, environmental triggers, and dysregulation of both innate and adaptive immune responses. Key cellular players—macrophages, fibroblast-like synoviocytes (FLS), T cells, and B cells—interact in the synovial environment, leading to cytokine overproduction, osteoclast activation, and chronic synovitis [3,4]. These interactions result in bone erosion, cartilage degradation, and loss of joint integrity.

Recent research has focused on identifying reliable biomarkers for RA diagnosis, disease activity monitoring, and prognosis. One such emerging biomarker is Dickkopf-1 (DKK-1), an inhibitor of the Wnt signaling pathway that plays a crucial role in bone homeostasis. Elevated serum levels of DKK-1 have been associated with increased joint destruction and reduced bone formation in RA [5]. Understanding the role of DKK-1 in RA pathogenesis could provide new insights into disease mechanisms and open avenues for both prognostic assessment and targeted therapy.

Pathophysiology of Rheumatoid Arthritis

The pathogenesis of rheumatoid arthritis (RA) is multifactorial, involving the interplay between genetic predisposition, environmental triggers, and immune system dysregulation. The immune response in RA initiates primarily in the synovial tissue, where both innate and adaptive immune mechanisms contribute to chronic inflammation and joint destruction [6].

Synovial macrophages and fibroblast-like synoviocytes (FLS) are central to the inflammatory cascade. These cells produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which perpetuate inflammation and activate osteoclasts, resulting in bone erosion [7]. FLS also express receptor activator of nuclear factor kappa-B ligand (RANKL), promoting osteoclastogenesis and bone resorption [8]. Simultaneously, matrix metalloproteinases (MMPs) degrade cartilage, further contributing to joint damage.

T cells, particularly CD4+ helper subsets, play a crucial role. Th17 cells secrete IL-17, stimulating FLS and enhancing inflammatory responses, while regulatory T cells (Tregs), which usually suppress immune reactions, are functionally impaired in RA [9]. B cells also contribute by producing

autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which form immune complexes and exacerbate synovitis [10].

The vascular endothelium in RA synovium becomes activated, increasing the expression of adhesion molecules and promoting leukocyte migration into the joint. Vascular endothelial growth factor (VEGF) further supports synovial angiogenesis and inflammation [11]. The net result is a vicious cycle of inflammation, tissue remodeling, and progressive joint damage.

Understanding these intricate immune interactions has led to the development of targeted therapies such as TNF inhibitors, IL-6 blockers, and JAK inhibitors, all aimed at disrupting specific pathways involved in RA pathophysiology.

Clinical Manifestations and Disease Assessment in Rheumatoid Arthritis

Rheumatoid arthritis (RA) typically begins with symmetrical polyarthritis, predominantly affecting the small joints of the hands, wrists, and feet. Patients often report joint pain, morning stiffness lasting more than 30 minutes, and swelling that can lead to joint deformities if left untreated [12]. As the disease progresses, classical deformities such as ulnar deviation, swan neck, and Boutonnière deformities may appear in chronic cases [13].

Beyond the joints, RA frequently involves extra-articular systems. Common manifestations include subcutaneous rheumatoid nodules, fatigue, anemia, and low-grade fever. Severe systemic complications may affect the cardiovascular, pulmonary, ocular, neurological, and renal systems. For instance, RA increases the risk of interstitial lung disease, scleritis, pericarditis, and accelerated atherosclerosis [14,15].

To evaluate disease activity, several validated composite indices are used. The Disease Activity Score using 28 joints (DAS28) combines tender and swollen joint counts, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, and the patient's global health assessment. A DAS28 score ≤ 2.6 indicates remission, while scores above 5.1 suggest high disease activity [16]. Other tools include the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI), which provide quick, reliable assessments, particularly in routine clinical practice [17].

Functional status is commonly assessed using the Modified Health Assessment Questionnaire (MHAQ) and Steinbrocker's functional classification. These tools provide insight into the patient's ability to perform daily activities and offer a standardized method to track disability over time [18,19]. Accurate assessment of disease activity and functional impairment is essential not only for monitoring treatment response but also for preventing long-term joint damage and disability.

Wnt Signaling Pathway in Autoimmune and Bone Diseases

The Wnt signaling pathway is a highly conserved molecular system that regulates embryonic development, cellular proliferation, differentiation, and tissue homeostasis. It plays a particularly

crucial role in bone biology by promoting osteoblast differentiation and inhibiting osteoclastogenesis, thus maintaining skeletal integrity [20].

Wnt signaling is classified into two major pathways: the canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. The canonical pathway is initiated by Wnt proteins binding to Frizzled (FZD) receptors and the co-receptors LRP5/6, leading to stabilization of β-catenin, its translocation to the nucleus, and activation of transcription factors such as TCF/LEF. These transcriptional changes enhance the expression of osteogenic and proliferative genes [21]. In contrast, the non-canonical pathways influence cell movement, polarity, and calcium signaling but do not involve β-catenin [22].

In the context of autoimmune diseases, aberrant Wnt signaling has been implicated in the pathogenesis of conditions like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS). In RA, inflammatory cytokines such as TNF-α and IL-6 can modulate Wnt signaling by upregulating antagonists like Dickkopf-1 (DKK-1), leading to suppressed osteoblast function and enhanced bone resorption [23]. This disruption contributes to joint erosion and systemic bone loss.

The pathway's dual role in inflammation and bone remodeling makes it an attractive target for research and potential therapy. Natural inhibitors of Wnt signaling include DKK-1, sclerostin, and secreted Frizzled-related proteins (sFRPs). Conversely, activators such as R-spondin proteins promote Wnt pathway activation and bone formation [24]. The balance between these regulators determines skeletal outcomes in health and disease.

Dickkopf-1 (DKK-1): Structure and Function

Dickkopf-1 (DKK-1) is a secreted glycoprotein that functions as a key antagonist of the canonical Wnt/β-catenin signaling pathway. It plays a vital role in embryonic development, bone formation, and adult tissue homeostasis [25]. The DKK family includes four members (DKK1–4), each of which contains conserved cysteine-rich domains. Among these, DKK-1 has been most extensively studied for its involvement in bone metabolism and immune regulation [26].

The DKK1 gene is located on chromosome 10q11 and encodes a 266-amino acid protein with a molecular weight of approximately 26 kDa. Structurally, DKK-1 contains two conserved cysteine-rich domains, separated by a linker region, and a C-terminal domain that shares structural similarity with colipase—a characteristic important for its receptor-binding function [27]. The protein folds into six secondary structures, including two alpha-helices and four beta-sheets, forming a compact 3D structure that interacts with low-density lipoprotein receptor-related protein 5/6 (LRP5/6) [28].

DKK-1 inhibits Wnt signaling by binding to LRP5/6 and preventing its interaction with Wnt ligands and Frizzled receptors. This action leads to degradation of β-catenin and suppression of downstream transcriptional activity [29]. Notably, DKK-1 can participate in a negative feedback loop, as it is itself

a downstream target of β-catenin/TCF-mediated transcription, allowing it to regulate Wnt signaling tightly [30].

Apart from its canonical inhibitory role, emerging evidence suggests that DKK-1 may also influence non-canonical Wnt signaling and activate other pathways such as the JNK and CKAP4-associated axes, thereby expanding its impact beyond bone homeostasis to include roles in inflammation, cancer biology, and tissue fibrosis [31].

In normal physiology, DKK-1 is expressed in adult tissues including bone, placenta, prostate, and spleen. However, its dysregulation is implicated in numerous pathological conditions, including osteoporosis, autoimmune diseases, and malignancies.

DKK-1 in Rheumatoid Arthritis

In rheumatoid arthritis (RA), the delicate balance between bone formation and resorption is severely disrupted, largely due to the chronic inflammatory milieu and the influence of pro-inflammatory cytokines. Dickkopf-1 (DKK-1) has emerged as a critical mediator in this process. Acting as a natural antagonist of the Wnt/β-catenin pathway, DKK-1 suppresses osteoblast differentiation and promotes osteoclast activation, contributing to bone erosion and impaired repair in RA-affected joints [32].

Tumor necrosis factor-alpha (TNF-α), a key cytokine in RA pathogenesis, directly upregulates the expression of DKK-1 in synovial fibroblasts. This leads to downregulation of osteoprotegerin (OPG), a decoy receptor that normally inhibits osteoclastogenesis by binding RANKL. The suppression of OPG, alongside increased RANKL expression, results in unchecked osteoclast activity and progressive bone resorption [33]. Moreover, high DKK-1 expression has been associated with elevated disease activity scores, radiographic joint damage, and markers of systemic inflammation in RA patients [34].

Animal models of RA have further supported the pathological role of DKK-1. Inhibiting DKK-1 with neutralizing antibodies protected against TNF-induced bone loss, enhanced osteoblast function, and increased the expression of osteogenic markers such as β-catenin and osteocalcin [35]. These findings underscore the potential of DKK-1 not only as a biomarker but also as a therapeutic target.

Importantly, serum levels of DKK-1 have been found to correlate with disease severity and functional impairment, indicating that DKK-1 could serve as a non-invasive indicator of joint remodeling and disability [36]. Its measurement may provide additional insights beyond traditional inflammatory markers, especially in patients undergoing biologic therapy.

The central involvement of DKK-1 in linking inflammation with skeletal damage highlights its value in the clinical assessment and potential modulation in RA management strategies.

DKK-1 in Other Autoimmune and Bone Disorders

While Dickkopf-1 (DKK-1) plays a significant role in the pathogenesis of rheumatoid arthritis, its dysregulation is also implicated in a variety of other autoimmune and bone-related diseases. In osteoporosis, elevated DKK-1 levels inhibit Wnt signaling and impair osteoblast function, leading to

decreased bone formation and increased fracture risk [37]. Mutations or overexpression of Wnt inhibitors like DKK-1 can disrupt bone homeostasis and are associated with low bone mineral density [38].

In osteoarthritis (OA), DKK-1 influences subchondral bone remodeling and osteophyte formation. Although its exact role remains complex, DKK-1 is believed to act as a negative regulator of abnormal bone growth in OA, modulating the response to mechanical stress and cartilage degeneration [39]. Elevated levels of DKK-1 in synovial fluid and serum have been observed in patients with advanced OA [40].

Ankylosing spondylitis (AS), a chronic inflammatory disease of the axial skeleton, shows an inverse relationship between DKK-1 levels and pathological new bone formation. Lower DKK-1 activity in AS may permit excessive Wnt signaling, thereby promoting syndesmophyte development and spinal ankylosis [41].

Systemic lupus erythematosus (SLE) and lupus nephritis (LN) are also influenced by Wnt pathway abnormalities. Overexpression of DKK-1 has been linked to altered renal extracellular matrix remodeling, glomerular dysfunction, and fibrosis, contributing to renal damage in LN patients [42].

In systemic sclerosis (SSc), DKK-1 expression is markedly downregulated in fibrotic skin lesions. This absence allows unopposed Wnt pathway activity, which contributes to fibroblast activation and excessive collagen deposition—a hallmark of SSc pathology [43].

Overall, the role of DKK-1 extends beyond RA, making it a shared modulator of inflammation and tissue remodeling across a spectrum of autoimmune and degenerative disorders. Its varied expression profiles in different diseases suggest disease-specific regulatory mechanisms and therapeutic implications.

Therapeutic Implications and Modulation of DKK-1

Given the central role of Dickkopf-1 (DKK-1) in modulating Wnt signaling and mediating inflammation-induced bone resorption, it has emerged as a promising therapeutic target in autoimmune and skeletal disorders. In rheumatoid arthritis (RA), the inhibition of DKK-1 could potentially reverse the destructive effects of inflammation on bone by restoring Wnt signaling, promoting osteoblast activity, and preventing osteoclast-driven erosion [44].

Preclinical studies using anti-DKK-1 monoclonal antibodies have demonstrated significant therapeutic benefits. In animal models of inflammatory arthritis and multiple myeloma, neutralizing DKK-1 led to increased bone mass, elevated expression of osteoblast markers such as osteocalcin, and decreased disease progression [45]. These findings provide a strong rationale for the development of DKK-1-targeted therapies, particularly in conditions characterized by excessive bone loss.

In addition to antibody-based interventions, other approaches such as DKK-1 gene knockout models and transgenic mice have been used to modulate DKK-1 expression. These models have consistently

shown enhanced bone formation and reduced skeletal damage, supporting the causative role of DKK-1 in bone pathologies [46].

Furthermore, modulation of DKK-1 may extend therapeutic benefits beyond the skeletal system. In fibrotic renal diseases, for example, DKK-1 gene therapy has been shown to suppress fibrotic markers such as fibronectin and type I collagen, indicating its anti-fibrotic potential [47]. Similarly, in neurodegenerative conditions like Alzheimer's disease, DKK-1 is upregulated in response to beta-amyloid toxicity, and targeting it may offer neuroprotective effects [48].

While clinical trials of DKK-1 inhibitors are still in early stages, these preliminary findings highlight the therapeutic versatility of targeting Wnt signaling. Careful modulation of DKK-1 could open new avenues in the treatment of autoimmune, metabolic, and degenerative diseases.

Conclusion and Future Perspectives

Dickkopf-1 (DKK-1) has emerged as a crucial link between inflammation and bone remodeling, particularly in the context of rheumatoid arthritis (RA). By antagonizing the Wnt/β-catenin signaling pathway, DKK-1 suppresses osteoblast function and promotes osteoclast-mediated bone resorption—mechanisms that contribute directly to joint erosion and functional decline in RA patients [49]. Elevated serum DKK-1 levels have shown strong associations with disease activity, radiological damage, and physical disability, underscoring its value as a potential biomarker for disease monitoring [50].

Beyond RA, the dysregulation of DKK-1 is implicated in numerous autoimmune and degenerative diseases, including osteoporosis, osteoarthritis, systemic lupus erythematosus, and systemic sclerosis. Its role extends to conditions such as Alzheimer's disease and chronic kidney disease, reflecting its systemic regulatory functions [51]. This broad spectrum of activity makes DKK-1 not only a diagnostic and prognostic marker but also an appealing therapeutic target across multiple clinical settings.

Future directions should focus on validating DKK-1 as a reliable biomarker in longitudinal cohorts, exploring its utility in predicting treatment response, and evaluating the safety and efficacy of DKK-1 inhibitors in human trials. In RA specifically, integrating DKK-1 level assessment into standard disease activity indices could enhance personalized treatment approaches.

Moreover, understanding the dual regulatory role of DKK-1 in both canonical and non-canonical Wnt signaling may uncover new therapeutic strategies that restore immune tolerance and bone homeostasis without impairing physiologic functions. As research continues, DKK-1 holds the potential to redefine current paradigms in autoimmune disease management and bone-targeted therapy.

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