Review article

Dickkopf 1 protein and its association with joint deterioration in rheumatoid arthritis: Systematic review

Alex Darío Cardona-Rincón a,*, Juan Manuel Bello-Gualtero b,c, Juan Carlos Munevar-Niño d, Consuelo Romero-Sánchez b,c,d, Rafael Raúl Valle-Oñate e

a Reumatología, Facultad de Medicina, Universidad Militar Nueva Granada, Bogotá, Colombia
b Servicio de Reumatología e Inmunología, Hospital Militar Central, Bogotá, Colombia
c Grupo de Inmunología Clínica, Universidad Militar Nueva Granada, Bogotá, Colombia
d Unidad de Investigación Básica Oral-UBO, Universidad el Bosque, Bogotá, Colombia
e Servicio de Reumatología e Inmunología, Clínica Colombiana de Reumatología, Rehabilitación e Inmunología, Salud Reinun, Bogotá, Colombia

A B S T R A C T

Background: Rheumatoid arthritis (RA) is an autoimmune disease that is mainly characterized by joint deterioration and decreased bone mineral density. The Dickkopf 1 protein (DKK1) exerts a negative regulatory function of the Wnt pathway involved in the differentiation of osteoblasts, and has been observed to be overexpressed in patients with RA.

Objective: To provide updated information on current knowledge about the relationship between DKK1 serum levels and the presence of bone and joint damage in RA patients.

Method: A qualitative systematic review was carried out in the PubMed, Embase, Cochrane and Scielo databases using the terms Dickkopf 1, DKK1, Dickkopf related protein 1, Rheumatoid Arthritis, and Bone biomarker.

Results: A total of 12 studies were chosen that met the requirements of the search. These included 7 prospective cohorts, 4 cross-sectional studies, and 1 clinical trial. Of the 12 studies reviewed, 10 analyzed the relationship between serum DKK1 levels and the presence of bone damage as the primary outcome. One of them analyzed this relationship as a secondary outcome and another one the RSP01/DKK1 ratio. The results to date seem to indicate that DKK1 could have an active role in advanced stages of RA, but not in the initial phase.

Conclusions: The DKK1 protein plays an essential pathophysiological role in the decrease of bone mass and joint remodelling, depending on the stage of the disease in patients with RA. Its role as a biomarker or therapeutic strategy would be an interesting alternative still under study.

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Keywords: Rheumatoid arthritis
Dickkopf 1
Biomarker
Bone resorption
Proteína Dickkopf 1 y deterioro osteoarticular en artritis reumatoide: revisión sistemática

RESUMEN

Antecedentes: La artritis reumatoide (AR) es una enfermedad autoinmune caracterizada principalmente por deterioro articular y disminución de la densidad mineral ósea. La proteína Dickkopf 1 (DKK1) ejerce una función reguladora negativa de la vía Wnt comprometida con la diferenciación de osteoblastos y se ha observado que puede estar sobreexpresada en pacientes con AR.

Objetivo: Proveer información actualizada sobre el conocimiento de la asociación entre los niveles séricos de DKK1 y la presencia de daño óseo y articular en pacientes con AR.

Método: Se realizó una revisión sistemática cualitativa en las bases de datos Pubmed, Embase, Cochrane y Sicio utilizando los términos Dickkopf 1, DKK1, Dickkopf related protein 1, rheumatoid arthritis, biomarker, resorción ósea.

Resultados: Se escogieron 12 estudios que llenaban los requisitos de la búsqueda; 7 fueron cohortes prospectivas, 4 estudios de corte transversal y uno ensayo clínico. De los 12 estudios revisados, 10 analizaron la asociación entre niveles séricos de DKK1 y presencia de daño óseo como desenclace primario. Uno de ellos analizó esta asociación como desenclace secundario y otro la relación RSP01/DKK1. Los resultados hasta la fecha parecen indicar que la DKK1 tendría un papel activo en estudios avanzados de AR y no en la fase inicial.

Conclusiones: La proteína DKK1 desempeña un papel fisiopatológico esencial en la disminución de la masa ósea y la remodelación articular, dependiendo de la fase de la enfermedad, en pacientes con AR. Su papel como biomarcador o estrategia terapéutica sería una interesante alternativa aún en estudio.

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease, characterized by chronic synovitis, joint deterioration, and excessive bone loss. It affects between 0.5 and 2% of the world population, and is more common in women, with a peak of presentation between 50 and 60 years old. The etiology of the disease is unknown; however, it is considered to be the result of the exposure to various environmental factors in genetically predisposed individuals. These genetic and environmental factors interact and trigger immune system alterations that lead to the production of antibodies such as the rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP), that finally result in the production of pro-inflammatory cytokines and the development of inflammatory arthritis. The loss of bone mass is a common characteristic in RA and it has been shown to be present since the early stages of the disease. In these patients, periarticular osteopenia is a significant characteristic. Furthermore, erosions at the pannus and adjacent bone tissue interphase may be identified, and these erosions progress rapidly and contribute to the deformities and morbidity that are typical of the disease. Since the severity and bone and joint involvement directly impact the short and long term prognosis in these patients, a large number of studies have tried to establish which factors identified early may predict negative outcomes. The major predictor of bone and joint deterioration in RA is the presence of erosions at the onset of the disease. However, our current knowledge, and the heterogeneity of the outcomes in patients with AR, make it mandatory to study new biomarkers to enable a more individualized treatment, addressed to therapeutic goals, which is currently referred to as T2T (treat to target) therapy. The recent evidence shows that DKK1 protein may play an active role in regulating bone biology.

Dickkopf 1 negative regulation of the Wnt pathway

The Wnt pathway activation induces different intracellular signals that are divided into two groups: the canonic or classical pathway and the non-canonic. The former is better known and presents an accumulation of β-catenin in the cytoplasm and subsequent translocation to the nucleus, where it modulates the transcription of various genes (Fig. 1A). Under baseline conditions, when it is not stimulated, a complex formed by several proteins such as axin, adenomatous polyposis coli (APC) protein, and glycogen synthase kinase-3β (GSK3β) may be found. GSK3β phosphorylates β-catenin making it susceptible to binding to ubiquitin and to be subsequently degraded in the proteasomes (Fig. 1B). In this manner, the intracellular levels of β-catenin are kept low. However, when the Wnt pathway is activated through the binding of the Wnt ligands to its receptor, the axin APC-GSK3β complex breaks down, reducing the phosphorylation activity of the GSK3β, and simultaneously reducing the phosphorylation of β-catenin and, consequently, its degradation in the proteasomes. Upon hypophosphorylation, it accumulates in the cytoplasm and translocates to the nucleus,
where it regulates the gene expression through the activation of transcription factors such as TCF/LEF\(^2\) of molecules involved with the differentiation, proliferation, and maturation of osteoblasts, such as fibronectin, connexin 43, periostin, and the retinoic acid receptor \(\gamma\).\(^{11}\) Wnt ligands act through the binding of receptors located in the cellular membrane (Fig. 1B). Several molecules with inhibiting action on the Wnt pathway have been described. The DKK1 inhibition of this pathway prevents the activation of the deshevelled protein (a protein associated with the Fzd receptor acting downstream), GSK3\(\beta\) continues to be activated and phosphorylates \(\beta\)-catenin, which then undergoes proteasomal degradation.\(^{7,12-14}\) 

**Dickkopf 1 structure and its association with low density lipoprotein receptor related protein 5/6 and Kremen**

The 3 members of the DKK family (DKK1, DKK2, DKK4) are effective antagonists of the canonic Wnt-\(\beta\) catenin signalling pathway by binding directly and with significant affinity to LRP 5/6.\(^{15,16}\) The DKK molecule contains 2 conserved cysteine-rich domains (N or C, in accordance with their localization in the protein); these are connected through a binding domain\(^2\) (Fig. 2); the C domains of DKK1 and DKK2 may on their own inhibit the Wnt pathway.\(^{18,19}\) Studies on mutagenesis have revealed that one side of the C domain of DKK2 binds to LRP 5/6, while the other binds to Kremen,\(^20\) a molecule that modulates the antagonistic effect of DKK on the Wnt pathway. Moreover, the LRP 5/6 molecule may be divided into 3 regions: the ectodomain (ECD), the transmembrane domain, and the cytoplasmic domain.\(^{21}\) The ECD of LRP 5/6 also contains 4 \(\beta\) helical (P) domains comprising 4 amino acids (Tyr-Trp-Thr-Asp); each of the helical components couples to a domain similar to the epidermal growth factor (EGF) and then the ECD is made up by 3 type A receptor molecules of low density lipoprotein (LA).\(^{21}\) Several studies on mutagenesis indicate that the different Wnt molecules bind to different regions of the ECD of LRP 5/6.\(^{22,23}\) According to these studies, it can also be inferred that the P-EGF 3 and 4 domains that make up the ECD of LRP 5/6 are not needed for the Wnt1 pathway signalling, but are essential for DKK1 inhibition.\(^{24}\) The reason is that in

**Fig. 2 – Representation 3D of the DKK1 protein structure.** The helices are shown in black and the folded blades are shown in dark grey colour. Schematic developed and modified by Paymol DLP 3D, Cod. RSGB 358V chain X. Sequence available in UniProtKB: 094907. Edited by Chila-M.L.2018.

the case of Wnt3a the binding surface to LRP 5/6 partially overlaps with the DKK1 binding site, so probably the antagonistic effect of DKK1 may be due to a mechanism of direct competition with the Wnt3a molecule for its binding site in LRP 5/6.\(^{25}\)

The objective of this systematic review was to contribute with updated information on DKK1 protein and its association with osteoarticular deterioration in patients with RA.

**Materials and methods**

A systematic literature review of experimental studies, analytical observational studies (cohorts), and cross-sectional studies was conducted in order to assess the role of DKK1 protein and its association with osteoarticular outcomes (for example, bone erosions, joint damage, reduced bone mineral density [BMD]) in patients with early (<2-years duration) or established RA. A search of primary studies, systematic
reviews, and meta-analyses was conducted in the most important scientific databases, using the MeSH terms for each of the components of the PICO question (Problem, Intervention, Comparator, Outcomes).

**Types of studies**

Controlled clinical trials, published and un-published cohort and cross-sectional studies written in English or Spanish, evaluating the association of the DKK1 levels with osteoarticular deterioration outcomes in patients with early or established RA were included. In all cases, the number of patients studied was more than 50. The analytical studies included all of the trials that considered exposure, target population and bias control strategies.

**Type of participants**

Patients older than 18 years with a diagnosis of early or established RA.

**Type of intervention**

Determination of the serum DKK1 levels.

**Type of outcomes**

Association of the serum DKK1 levels with bone erosions, decreased BMD or joint damage.

**Electronic search**

A database search was conducted using the above-mentioned PICO strategy. The Medline search was conducted with a combination of key words and filters recommended by Pubmed. The search was limited to articles published in English and Spanish.

**Search terms**

A structured literature search was conducted using the electronic databases Pubmed, Embase, Cochrane and Scielo, with the key words «(Arthritis, Rheumatoid-[Mesh]) AND «DKK1 protein, human» [Supplementary Concept]) AND «Bone Resorption-[Mesh] AND «Biomarker».

**Selection of studies**

The abstracts of the articles identified were reviewed to eliminate any irrelevant articles. Subsequently, any articles chosen were independently reviewed by the authors ACR and JBG, to check for compliance with the inclusion criteria (Fig. 3).

**Data mining**

The studies that met the inclusion criteria were analyzed for data mining. The data were independently extracted by 2 of the authors (ACR and JBG) and the results were then re-assessed by the other authors (JCM, RVO and CRS) for

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**Fig. 3 – Flow diagram for screening and selection of evidence.**
一致的。来自每个研究的数据被总结在2个表中，用于早期和已建立RA的患者，分别包括患者的人数，年龄，性别，影像学评分，类型，骨关节炎结局，频率测量和关联和统计学意义。

meta-分析没有按性别进行，因为数据的不一致性。这些数据从每个研究中提取，被总结在2个表中，用于早期和已建立的RA，分别包括患者的数量，年龄，性别，影像学评分，类型，骨关节炎结局，频率测量和关联和统计学意义。

**Missing data**

有些研究未能报告DKK1水平和其他研究未能报告与频率和关联。在后者的案例中，统计学意义被用来比较直接结果的研究。

在同一组研究中，一个前瞻性队列研究在136例已建立的RA患者中进行，其中在基线HGF和DKK1水平被测量，添加到一个基线断层摄影研究中，该研究在1, 2和5年时重复。在该研究中，基线DKK1水平与增加的脊椎骨丢失在一年内有关，该结果在完成多变量分析后被保持。在研究中，Choi et al. 2014年发现，只有RA和放射学进展的疾病在不同变量下有显著增加的DKK1水平和DKK1/R-Spondin(DKK1受体)。在多变量分析中，DKK1水平单独与放射学进展无关，但DKK1/R-Spondin指数有关。

最后，在2015年Rossini et al.的进行的一个横断面研究中，在154例已绝经的女性中，匹配年龄，性别，体重指数(BMI)和维生素D水平，DKK1水平被测量和放射学评价被进行，添加到测量脊柱和髋骨密度(BMD)的。结果表明，在患有RA的患者中，年龄和DKK1水平，PTH水平和疾病的发生在患者中骨侵蚀显著增加。38

**Results**

用搜索词查询，839条标题被识别在各种数据库中，814条被排除在应用了适用性的标准和摘要后。然后任何双倍研究被排除，并且，3个研究被排除，增加了符合骨关节炎结局的被排除。在12个研究中，11个被写成英文，1个被写成西班牙文，7个是前瞻性的队列研究，4个是横断面研究，并且1个是临床研究。在研究的10个分析中，10个分析的DKK1和骨损伤的存在被认为是主要的 outcome。其中一个分析了这个作为次级 outcome然而另一个分析的，RSPO1/DKK1比率。

**Relationship between the Dickkopf 1 levels and osteoarticular damage in early rheumatoid arthritis**

在2008年，Garnero et al.进行了一项前瞻性研究，113名患者有早期RA，他们正在接受治疗。在DKK1水平被测量和与骨质疏松的放射学随访进行与Sharp-van der Heijde(SvH)评分1年。他们发现早期的DKK1水平与骨侵蚀的风险增加，这些变化与年龄，性别，骨关节炎的放射学损害，CRP水平或者疾病活动有关。

随后，Liu et al. 2014年分析的DKK1水平和骨保护蛋白在150名早期RA患者和150名已建立的RA患者中，他们发现早期的DKK1水平与增加的骨损坏的SvH评分和临床活动基于DAS28指数在已建立的RA患者中。

More recently, Seror et al. 2013年分析的法国患者中使用了ESPOIR。在这个前瞻性研究中，DKK1基线水平，急性期反应物，一个诊断测量的疾病活动和一个在2-年评价的骨损坏基于SvH水平的骨损伤。总共有110例患者有RA，患有骨侵蚀是在随访的开始，这个发现与多个因素相关，包括抗-CCP，年龄，性别，升高CRP，ESR和DKK1水平。在多变量分析中，DKK1水平与放射学进展相关的有骨损伤的SvH。28

在2013年，de Rooy et al.进行了一项单核苷酸多态性(SNP)研究的不同的Wnt通路的4个欧洲队列(Leiden NED, Groningen NED, Sheffield-UK and Lund-SWE)，在8个SNP中，DKK1, 44的LRP-5, 16的Kremen-1和9的骨形成蛋白(SOST)被分析，和回归模型被进行来建立这些多态性的分子和它们的序列水平，以及放射学进展使用2个评分(SvH和Larsen)。结果表明，在Leiden队列中，6个SNP中，DKK1, 3的SOST，Kremen和LRP-5是显著增加的，与关节损伤的进展相关。根据meta-分析进行的，3个SNP中，DKK1是显著增加的和与关节损伤的进展，2个SNP中，SOST有趋向于统计学意义。一个SNP被与较高的DKK1水平相关(r=1896368, p=0.02)。

A study by Miceli-Richard et al. 2015年尝试模拟发现的结果由de Rooy et al.在法国队列ESPOIR;然而，10个SNPs中，DKK1研究中是相关的和放射学进展的结构损害相关的SvH评分。30

进一步研究未能发现骨损伤中DKK1和放射学改变在早期RA患者中的关系。31

Gómez-Vaquero et al. 2016年分析的97例早期RA(中位年龄1.6年)患者。根据平均随访的3.3年，平均SvH评分的增加是0.88±2.2单位。多变量分析显示了某些因素如年龄(OR per year = 1.10, p=0.003)和高等CRP(OR = 1.29; p=0.005)，但不是DKK1水平，与放射学进展相关的在SvH。31
**Table 1 – Studies on the association between serum DKK1 levels and bone damage in early RA.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Sex (F)</th>
<th>Age (years)(median±DS)</th>
<th>Radiological method</th>
<th>Outcome</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garnero et al. 26</td>
<td>Cohort</td>
<td>113</td>
<td>75%</td>
<td>50±13</td>
<td>Modified Sharp</td>
<td>Increased DKK1 and &gt; risk of bone erosion progression</td>
<td>p &lt; 0.004</td>
</tr>
<tr>
<td>Liu et al. 27</td>
<td>Cross-sectional</td>
<td>150</td>
<td>70.6%</td>
<td>47.57±13.55</td>
<td>SvH</td>
<td>DKK1 unrelated to bone damage in early RA</td>
<td>Data not available</td>
</tr>
<tr>
<td>Seror et al. 28</td>
<td>Multicenter cohort</td>
<td>813</td>
<td>78.2%</td>
<td>48.5±12.3</td>
<td>SvH</td>
<td>Higher DKK1 baseline levels in patients with bone progression by SvH</td>
<td>p &lt; 0.04</td>
</tr>
<tr>
<td>Gómez-Vaquero et al. 31</td>
<td>Cohort</td>
<td>97</td>
<td>70%</td>
<td>53±14</td>
<td>SvH</td>
<td>DKK1 levels not associated with radiological progression at 3 years</td>
<td>p = 0.548</td>
</tr>
<tr>
<td>Wechaleckar et al. 32</td>
<td>Cohort</td>
<td>50</td>
<td>76%</td>
<td>ND</td>
<td>SvH</td>
<td>DKK1 levels not associated with radiological progression by SvH</td>
<td>Data not available</td>
</tr>
<tr>
<td>Cardona-Rincón et al. 33</td>
<td>Cross-sectional</td>
<td>63</td>
<td>76.7%</td>
<td>49.57±11.3</td>
<td>SENS</td>
<td>DKK1 levels not associated with the presence of erosions according to SENS score</td>
<td>p = 0.867</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; DKK1: Dickkopf 1; F: sex female; NA: not available; SENS: Simple Erosion Narrowing Score; SvH: Sharp-van der Heijde score.
Similarly, Wechalekar et al., in 2016, conducted an initial cohort study in 50 patients with RA of <1 year of evolution, with double positivity for RF and anti-CCP. No association was found between the baseline levels of DKK1 and the radiological progression according to SvH, after one year of follow-up.  

Finally, in 2017 Cardona-Rincón et al. submitted the results of a cross-sectional trial in 63 patients with early RA. Once again, no significant statistical correlation was found between the levels of DKK1 and variables such as the disease activity according to DAS28 or radiological damage based on the SENS score. 

**Relationship between the Dickkopf 1 levels and osteoarticular damage in established rheumatoid arthritis**

Other studies aimed at establishing a correlation between the elevated levels of DKK1 and osteoarticular deterioration have been conducted in patients with established RA (Table 2).

Three cohorts, 2 cross-sectional studies, and a clinical trial studied the association between DKK1 and bone outcomes in established RA.

In 2011, a group of researchers led by Doctors Wang and Liu analyzed the levels of DKK1 in serum of 100 patients with established RA and 100 patients with other rheumatologic conditions such as osteoarthritis and ankylosing spondylitis, and found that the levels of this protein were significantly elevated in the RA group. Moreover, the levels of DKK1 correlated with the levels of CRP, ESR, and radiological changes according to the SvH score. This study also observed that patients with RA that were treated with anti TNF-α (infliximab) or anti-IL-1 (anakinra) presented decreased serum DKK1 levels.  

Also in 2011, Grandaunet et al. conducted a prospective cohort study in 136 patients with established RA, with an average duration of the disease of 2.2 years. DKK1 serum levels and hepatocyte growth factor (HGF) were measured, and a radiological evaluation was conducted with the SvH score. This study found that elevated HGF levels but not the DKK1 levels were associated with osteoarticular damage.

**Discussion**

RA is an autoimmune, inflammatory, chronic, and progressive disease, mainly characterized by damage to the small joints of the hands and feet and a generalized reduction in BMD. From the onset of the disease, patients may experience bone erosions; it is well known that the presence of bone erosions is the most important predictor for the occurrence of future erosions and bone deterioration, and is also associated with decreased BMD. Furthermore, the presence of certain factors such as elevated acute phase reactants, the number of swollen joints, the presence of RF or anti-CCP, female gender, the prevalence of upper rather than lower extremities involvement, age, and altered BMI, has shown to be associated with progression of radiological damage in patients with RA. Not all patients with RA have the same pattern of bone damage progression; hence the vital importance of being able to differentiate which patients will experience worse outcomes, in order to optimize resources and improve the clinical results.

The knowledge of the components of the Wnt osteogenic (canonic) pathway and its negative regulators has improved over the past years. The role of DKK1 protein, as a molecule that plays different roles, has given rise to a lot of interest among the scientific community and has led to an increasing number of studies published about this molecule as a serological marker associated with different outcomes in different diseases, both rheumatologic such as ankylosing spondylitis, systemic lupus erythematosus, or osteoarthritis, and non-rheumatologic such as hepatocellular carcinoma, atherosclerotic disease and diabetes, inter alia. DKK1 studies have been made in RA, both in the synovial fluid and in the bone; these studies have established the overexpression of this protein in the sites most affected by the pathology, which is irrefutable proof of the time and space relationship between DKK1 and the clinical or radiological findings in patients with RA. There is a very close relationship between elevated TNF-α and DKK1 levels in patients with RA, and it has been shown that cytokines such as TNF-α and IL-1β may indirectly stimulate the production of DKK1 through the fibroblast-like synovocytes. Likewise, the treatment with anti-TNF-α antibodies in these patients has been associated with a decrease in the serum levels of DKK1, in the same way as with anti-IL-6 antibodies. This shows that the DKK1 levels may play an important role, not just in predicting bone outcomes, but also in the evaluation of the response to anti-TNF-α or anti-IL-6; however, proper studies are needed to be able to answer this question.

The results of the different studies analyzed in this systematic review show that DKK1 protein may be an additional tool for the clinician, in order to identify those patients that require more aggressive therapy. Nonetheless, there is little evidence in patients with early RA because of the short time of evolution, keeping in mind the importance of forecasting outcomes from the onset of the disease. It must be said also that while the DKK1 levels are associated with bone erosions or mineral reduction, there was no significant association in these studies with the reduction in the joint space, which is consistent with the current knowledge about the involvement of the Wnt pathway rather than its negative regulators (DKK1, sclerostin) in joint remodelling of patients with RA.

This review tried to divide the current RA DKK1 into two groups: patients with early RA and patients with established RA. However, since currently no consensus has been reached on the cut off point between the early and the late presentation of the disease, it was decided to classify the studies in accordance with the opinion of the authors thereof (for instance, in some studies, early RA was established as a disease duration of <2 years, while in others it was <1 year or <6 months). Another drawback of the serum DKK1 studies is that most of them measure the circulating DKK1 instead of the functional DKK1 (DKK1 bound to LRP 5/6). According to some authors, functional DKK1 correlates better with the bone resorption status in contrast to circulating DKK. Moreover, these studies have shown that most of the patients who overexpress DKK1 experience bone damage progression; however, it is yet unknown why some patients with normal or low DKK1 levels exhibit progression of radiological damage. It should also be mentioned that whilst some of the trials conducted so far have shown an association of DKK1 with progression of radiological damage,
Table 2 - Studies on the association between serum DKK1 and bone damage in established RA.

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Sex (F)</th>
<th>Age (years)(median±SD)</th>
<th>Radiological method</th>
<th>Outcome</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al.(^{27})</td>
<td>Cross-sectional</td>
<td>150</td>
<td>74%</td>
<td>46.77 ± 11.66</td>
<td>SvH</td>
<td>Levels. Increased DKK1 associated to a higher Sharp score in established RA</td>
<td>(p = 0.000)</td>
</tr>
<tr>
<td>Wang et al.(^{34})</td>
<td>Clinical trial</td>
<td>100</td>
<td>90%</td>
<td>50 ± 28</td>
<td>Sharp</td>
<td>Increased DKK1 associated with the presence of bone erosions</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Grandaunet et al.(^{35})</td>
<td>Cohort</td>
<td>136</td>
<td>76%</td>
<td>51.3 ± 12.1</td>
<td>SvH</td>
<td>DKK1 unrelated too bone damage at 1, 2, 5 and 10 years</td>
<td>(p = 0.16)</td>
</tr>
<tr>
<td>Grandaunet et al.(^{36})</td>
<td>Cohort</td>
<td>136</td>
<td>76%</td>
<td>51.3 ± 12.1</td>
<td>N/A</td>
<td>Higher baseline DKK1 levels in patients with hand bone loss at 1 year</td>
<td>(p = 0.022)</td>
</tr>
<tr>
<td>Choi et al.(^{37})</td>
<td>Cohort</td>
<td>102</td>
<td>89.2%</td>
<td>52.5 ± 12.9</td>
<td>SvH</td>
<td>Increased DKK1/RSPO1index associated with radiological progression with SvH</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Rossini et al.(^{38})</td>
<td>Cross-sectional</td>
<td>154</td>
<td>100%</td>
<td>65 ± 7</td>
<td>N/A</td>
<td>Higher DKK1 levels in patients with bone erosions</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; DKK1: Dickkopf 1; DXA: dual X-ray absorptiometry; F: female gender; N/A: not applicable; RSPO1: R-spondin 1; SvH: Sharp-van der Heijde score.
other studies such as those by Grandaunet et al., Gómez-Vaquero et al. and Liu et al., were not able to establish this association in the early RA subgroup. A likely explanation for this discrepancy could be the broad heterogeneity of the population studied, keeping in mind differences in the laboratory parameters of the DKK1 levels, dissimilar populations studied, the duration of the disease, the concomitant biological or glucocorticoid therapy, inter alia. Additionally, the multiple and potential causes of pre-analysis alterations, such as diurnal variations, the comorbidities of the patient, and the technical conditions under which the measurements were taken, should be taken into consideration.

Conclusions

Several studies have been conducted, both in early and established RA patients, that have associated elevated serum DKK1 levels with adverse outcomes, including increased radiological progression of bone damage or decreased bone mass according to densitometry. Protein DKK1 plays a pathophysiological role in bone mass reduction and joint remodelling in patients with RA. Its role as a biomarker or therapeutic strategy in this population has not yet been established. The results to date seem to indicate that DKK1 could play an active role as a biomarker in advanced RA stages, but not in the initial phase.

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Conflict of interest

The authors do not have any conflict of interests to disclose.

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REFERENCES


