Original Article

Correlation of Circulating Dickkopf-1 Level with Sonographic Findings and Radiographic Grading in Primary Knee Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is a frequently complex joint disease that involves all joint components, including cartilage degeneration and new bone development. Dickkopf-1 (Dkk-1) regulates bone growth and repair in OA. The purpose of this study is to determine Dkk-1 blood levels in individuals with primary knee joint OA, as well as their associations with disease progression and severity. **Methods:** This study included 45 individuals with primary OA of the knee and 45 healthy participants. Demographic data, body mass index, Visual Analog Scale, and Western Ontario and McMaster Universities Arthritis questionnaire scores were gathered. On radiography, the Kellgren and Lawrence score was acquired. The knee joint ultrasonography results were documented. The blood level of Dkk-1 was determined using the enzyme-linked immunosorbent assay method. **Results:** Dkk-1 levels in the blood were substantially higher in patients with OA than in healthy persons. Serum Dkk-1 levels appeared to have a significantly inverted relationship with radiological OA grades in knee OA ($P < 0.001$). Dkk-1 serum levels were significantly lower in individuals with ultrasonographic knee effusion (median = 3.2, interquartile range [IQR] = 3.1–4.16) than in those without effusion (median = 4.79, IQR = 4.04–5.09). Furthermore, there was a strong correlation between Dkk-1 levels and ultrasonographically measured femoral cartilage thickness. **Conclusion:** Dkk-1 is an interesting radiological indicator associated with degenerative articular joint disease. It may have a crucial function in slowing the process of degeneration in knee OA and reflecting the disease's radiographic and clinical severity.

Keywords: Dickkopf-1, Kellgren–Lawrence, osteoarthritis, Western Ontario and McMaster Universities Arthritis Index

Introduction

Osteoarthritis (OA) constitutes one of the most frequently encountered types of joint disorders, which includes articular cartilage degeneration, aberrant remodeling of the bones, and osteophyte formation, all of which contribute to persistent discomfort and limited mobility in the afflicted joints. The knee joint is a particularly clinically significant location for initial OA engagement. The vast majority of persons with OA have radiographic proof by the age of 65 years, and roughly 80% of those above the age of 75 years are afflicted.[1] Radiological examination, which represents the severity of OA by grading the joint degradation,[2] is one of the current approaches for evaluating the damaged joint. The Kellgren–Lawrence (K-L) Grading Scale for severity of the disease[3] has been the most frequently employed method.

Wingless (Wnt) signaling pathway-released glycoproteins serve as significant regulators of cellular development and response to mechanical loading. The ligands for Wnt begin communication through interaction with a coreceptor complex consisting of low-density lipoprotein receptor-related protein (LRP) 5 or 6 and frizzled proteins. Activation of receptors in the canonical Wnt/β-catenin signaling pathway causes β-catenin to

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stabilize and aggregate in the nucleus, ultimately leading to the expression of specific osteoblastic genes necessary for bone formation. Dickkopf-1 (Dkk-1) acts as a direct inhibitor of the Wnt signaling pathway, functioning as a crucial modulator of bone formation that regulates skeletal development throughout early embryonic growth.[4]

Numerous cytokines have been extensively studied in serum or in synovial fluid in those with OA of the knee in quest of molecular indicators that might predict the extent and progression of the disease.[5-7] However, research on the possible link between Dkk-1 blood levels and disease progression in primary OA of the knee joint has been conflicting.[8]

We investigated the blood levels of Dkk-1 in individuals with knee OA and normal controls to determine its clinical relevance in disease progression, as well as whether there is a link between Dkk-1 in the blood and the sonographic and radiographic grading of knee OA.

Methods

Study participants

The study included 45 individuals with primary knee OA (36 females and 9 males; mean age: 53.08 ± 4.2 years) who met the criteria set by the American College of Rheumatology for knee OA.[9] We recruited 45 gender- and age-matched individuals managed in outpatient clinics for causes aside from knee problems and exhibited normal knee radiographs (35 females and 10 males; mean age: 52.2 ± 3.6 years) as controls. No one in the study had diabetes, a history of corticosteroid local injections, cancer, traumatic knee injuries, an acutely inflamed joint, or other chronic inflammatory disorders.

All of our patients had a comprehensive medical history, physical assessment, and evaluation of function using the Western Ontario and McMaster Universities Arthritis (WOMAC) Index[10] and the Visual Analog Scale (VAS) score.[11] Weight-bearing anteroposterior X-rays of the involved knee joint were employed to grade the OA using the K-L rating system.[3] Grade 1: suspicious reduction of the joint space; grade 2: defined bone spurs and probable joint space narrowing; grade 3: moderately numerous bone spurs, distinct joint space narrowing, and sclerosis; grade 4: significant bone spurs, defined joint space narrowing, and significant sclerosis, as well as bone deformity.

Knee ultrasound

A rheumatologist with 5 years of expertise in musculoskeletal ultrasonography conducted the ultrasound (US) examination. All ultrasonographic examinations were done using the linear probe Toshiba Aplio 400 (Toshiba Medical Systems, Otawara, Japan). With the patient's knee bent and a cushion beneath the knee for comfort, a US examination of the suprapatellar recess was performed. After liberally applying gel to the suprapatellar region, scanning was performed in the longitudinal plane with a knee flexion of 30°. Fluid collection within the joint (>4 mm) was defined as an effusion, which is seen as a displaceable substance within the knee joint that is either hypoechoic or anechoic.[12]

After asking the patient to fully flex the joint, the probe was positioned vertically to the femur and just above the patella to assess the degree of femorotrochlear articular cartilage degradation. The femoral trochlea's V-shaped hypoechoic hyaline cartilage was examined with the knee in full flexion. The distance between the surface of the cartilage and the subchondral bone was used to determine the cartilage thickness. The thicknesses of the trochlear cartilage medial and lateral condyles of the femur were measured and expressed in millimeters.

Laboratory method

To quantify the Dkk-1 blood levels by enzyme-linked immunosorbent assay method, serum samples from all patients with knee OA and the control participants were collected in accordance with the manufacturer's instructions (Shanghai Korain Biotech Co., Ltd.). Standards containing recombinant human Dkk-1 and blood samples were added to 96-well microtiter plates precoated with Dkk-1-specific mouse monoclonal antibodies. The plates were then incubated at room temperature for 60 min. A goat-derived polyclonal antibody toward Dkk-1 was then incubated in each well for 2 h at ambient temperature after five rounds of washing with washing buffer. Following five washes, the solution containing the substrate was added to each well, and the entire plate was allowed to incubate for 10 min in a dark environment at ambient temperature. By employing the stop solution to stop the reaction, absorbance at 450 nm was measured using an automated microplate reader. A standard curve is obtained by plotting the concentrations of standards versus the absorbance.

Every single participant signed a written consent form before taking part in the study. The Research Ethics Committee at our institute approved this study with approval number 0000018. It follows the Helsinki Declaration's Ethical Principles. Each medical record, including all questions, was assigned a unique number, ensuring the confidentiality of all patient data.

Analysis

The data analysis was performed using version 24 of the Statistical Program for Social Science (SPSS, IBM Inc., Armonk, NY, USA). The frequency and percentage values were used to report the qualitative data. Quantitative values were presented as mean ± standard deviation (SD) for normally distributed data or as median (interquartile range [IQR]) for nonnormally distributed data. A measure of statistical dispersion, or the spread of data, is the (IQR). It is described as the variation between both the 25th and 75th percentiles of the data. When comparing two groups with regularly distributed data, the independent sample *t*-test (T) was used; however, the Mann–Whitney *U*-test was used to compare two groups whose data were abnormally distributed. A one-way analysis of variance compares more than two groups when the data are regularly distributed. The nonparametric data were compared using the Chi-square test. Pearson's correlation coefficient (*r*) test was utilized to determine the correlation between the data. Positive predictive value, negative predictive value, sensitivity, specificity, and cutoff values were all determined

using the receiver operating characteristic curve (ROC curve). Significant *P* values were those that were below 0.05. *P* values were considered highly significant if they were under 0.001. The means ± SD are used to represent all values.

Results

Demographic, clinical, and laboratory data of the studied groups

This study comprised 45 primary knee OA patients (36 females (80%) and 9 men [20%]) (Group A) diagnosed with knee OA using the 2016 updated criteria, as well as 45 healthy controls (Group B). OA patients had a mean age of 53.08 ± 4.2 years, a mean disease duration of 6.2 ± 2.6 years, and a mean body mass index (BMI) of 30.4 ± 3.07 kg/m^2, while the healthy control group had a mean age of 52.2 ± 3.6 years [Table 1]. There was no statistically significant difference (P = 0.313) in age, gender, or BMI between the two groups tested. The average VAS and WOMAC scores were 5.9 ± 1.5 and 60 ± 11.4, respectively.

Dkk-1 in Group A was statistically significantly higher (median = 4.09, IQR = 3.17–4.85) than in Group B (median = 2.4, IQR = 2.09–3.15) (P < 0.001). The ROC curve [Figure 1] shows that serum Dkk-1 may be employed to differentiate Group A patients at a cutoff level of >3.11, with 82.2% sensitivity and 75.6% specificity (area under the ROC curve = 0.92 and P < 0.001).

Comparison between Kellgren–Lawrence grades and the studied variables

Based on the K-L Scale, 13 patients had K-L grade 2 OA, 17 had K-L grade 3, and 15 had K-L grade 4. There was a very statistically significant rise in age in K-L grade 4 patients (58 ± 2.3) in comparison to K-L grade 3 patients (52.5 ± 1.4) and K-L grade 2 patients (48.2 ± 1.4) (P < 0.001). There was no statistically significant relationship between K-L grade and either gender or BMI (P = 0.338 and 0.142, respectively). Increased disease duration in K-L grade 4 patients (8.7 ± 2.3) was highly statistically significant as compared to K-L grade 3 patients (6.2 ± 1.1) and K-L grade 2 patients (3.3 ± 0.9) (P < 0.001) [Table 2].

In Table 2, K-L grade 4 patients showed rather statistically significant higher VAS and WOMAC scores (P < 0.001) when compared to K-L grade 3 patients (5.9 ± 0.7 and 58.8 ± 4.2) and K-L grade 2 patients (4.2 ± 0.4 and 46.2 ± 2.9).

In terms of sonographic findings of the afflicted knee, K-L grade 4 patients (12 patients, 80%) and K-L grade 3 patients (9 patients, 52.9%) had a significantly higher proportion of effusion than K-L grade 2 patients (0 patients,

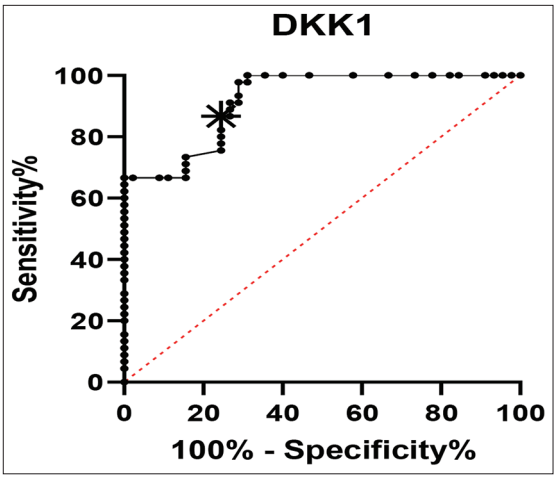

Figure 1: Receiver operating characteristic curve of Group A regarding serum dickkopf-1. Dkk-1: Dickkopf-1

Table 1: Comparison of clinical, laboratory, and demographic characteristics between the groups

	Group A (n=45)	Group B (n=45)	Statistics test	P
Age (years), mean±SD	53.08±4.2	52.2±3.6	t=1.01	0.313
Sex, n (%)				
Male	9 (20)	10 (22.2)	χ^2=0.067	0.796
Female	36 (80)	35 (77.8)		
BMI (kg/m²), mean±SD	30.4±3.07	29.7±2.5	t=1.1	0.273
Disease duration (years)				
Mean±SD	6.2±2.6			
Minimum–maximum	2–15			
VAS score				
Mean±SD	5.9±1.5			
Minimum–maximum	4–8			
WOMAC score				
Mean±SD	60±11.4			
Minimum–maximum	42–78			
Dkk-1 (ng/dL)				
Median	4.09	2.4	MW=162	<0.001 HS
IQR	3.17–4.85	2.09–3.15		

SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Arthritis, Dkk: Dickkopf-1, HS: Highly significant, MW: Mann–Whitney *U*-test

Table 2: A comparison of Kellgren and Lawrence grades and the studied variables in Group A

	K-L grade			Statistics test	*P*
	II (*n*=13)	III (*n*=17)	IV (*n*=15)		
Age (years), mean±SD	48.2±1.4	52.5±1.4	58.0±2.3	*F*=113.8	<0.001 HS
Sex, *n* (%)					
Male	1 (7.7)	5 (29.4)	3 (20)	χ^2=2.1	0.338 NS
Female	12 (92.3)	12 (70.6)	12 (80)		
BMI (kg/m^2), mean±SD	29.0±2.9	30.7±2.3	31.2±3.7	*F*=2.04	0.142 NS
Duration (years)					
Mean±SD	3.3±0.9	6.2±1.1	8.7±2.3	*F*=39.2	<0.001 HS
VAS score, mean±SD	4.2±0.4	5.9±0.7	7.5±0.6	*F*=102.1	<0.001 HS
WOMAC score, mean±SD	46.2±2.9	58.8±4.2	73.5±2.9	*F*=217.4	<0.001 HS
Effusion, *n* (%)					
No	13 (100)	8 (47.1)	3 (20)	χ^2=18.3	<0.001 HS
Yes	0	9 (52.9)	12 (80)		
MC thick, mean±SD	1.82±0.07	1.55±0.10	1.11±0.17	*F*=121.1	<0.001 HS
LC thick, mean±SD	2.00±0.08	1.75±0.11	1.51±0.16	*F*=54.2	<0.001 HS

K-L: Kellgren and Lawrence, SD: Standard deviation, BMI: Body mass index, VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Arthritis, LC: Lateral condyle, MC: Medial condyle, HS: Highly significant, NS: Not significant

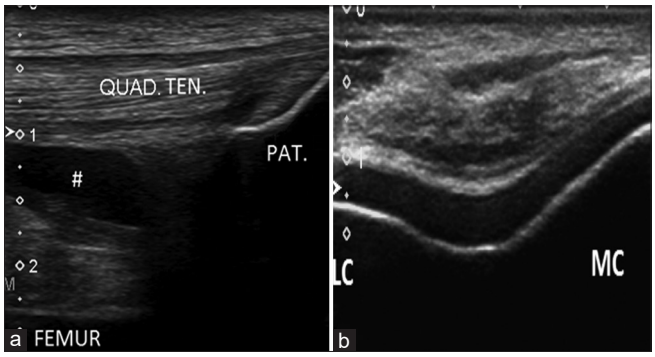

Figure 2: The pathologies of some of the study participants. (a) Ultrasound scan of the suprapatellar pouch of the knee demonstrating an effusion, (b) Sonographic image of the femoral articular cartilage at the level of the trochlear groove shows that the cartilage of the medial femoral condyle is thinner than the lateral condyle. (#). QUAD TEN: Quadriceps tendon, PAT: Patella bone, MC: Medial condyle, LC: Lateral condyle

0%). Regarding sonographic femoral cartilage thickness, K-L grade 4 patients had significantly lower medial and lateral condyle thickness (1.11 ± 0.17 and 1.51 ± 0.16) as compared to K-L grade 3 patients (1.55 ± 0.1 and 1.75 ± 0.11) and K-L grade 2 patients (1.82 ± 0.07 and 2.0 ± 0.08) [Figure 2] depicts an example of pathologies identified in the study participants.

Correlation of dickkopf-1 with the radiographic and sonographic data

Dkk-1 circulating levels have been determined and compared to radiological K-L grading and the ultrasonographic characteristics of knee OA. Dkk-1 was found to be significantly higher in K-L grade 2 patients (5.3 ± 0.15) as compared to K-L grade 3 patients (4.09 ± 0.14) and K-L grade 4 patients (3.7 ± 0.14). Reduced serum Dkk-1 levels were shown to be highly statistically significant in patients with effusion (median = 3.2, IQR = 3.1–4.16) as compared to individuals without effusion (median = 4.79, IQR = 4.04–5.09). Furthermore, a significantly strong beneficial correlation (r = 0.89 and 0.81, P < 0.001) between Dkk-1 and medial and lateral condyle thickness was found [Table 3].

Discussion

Although a number of studies have been conducted to gain insight into Wnt's role in OA, the exact mechanisms of the Wnt protein remain unclear. The potential ability of Wnts to alter bone development, endochondral ossification, bone expansion, and repair reflects its role in OA.[13]

The signaling pathway mediated by Wnt is regulated by various innate inhibitors, and decreasing the circulating levels of particular inhibitors may slow down the degree of OA progression. Dkk-1 serves as a Wnt suppressor, and its increased expression can diminish cartilage breakdown and the development of OA in mouse models driven by medial meniscus destabilization. Dkk-1 is capable of inhibiting Wnt-mediated transcription of certain genes such as Runx-2, Matrix metalloproteinases (MMPs), and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) 4 and 5.[14-16]

The key finding of the present study was that individuals with primary knee OA had greater blood levels of Dkk-1 than controls.

Our findings agree with the findings reported by Ibrahim *et al*.,[17] who demonstrated that OA patients had considerably greater blood levels of Dkk-1 than healthy persons (P < 0.001).

While Hassan and Behiry[18] observed a lack of statistical significance in the blood levels of Dkk-1 between individuals with knee OA and normal controls, Honsawek *et al*.,[2] Voorzanger-Rousselot *et al*.,[19] and Min *et al*.[20] stated that blood levels of Dkk-1 were considerably lower among OA individuals when compared to healthy subjects. Similarly,

Table 3: Correlation of dickkopf-1 with the radiographic and sonographic features in the patient group

	Dkk-1	Test	*P*
K-L grade			
II (*n*=13)	5.3±0.15	*F*=603.5	<0.001 HS
III (*n*=17)	4.09±0.14		
IV (*n*=15)	3.07±0.14		
Effusion			
No (*n*=24)	4.79 (4.04–5.09)	MW=105.5	0.001 HS
Yes (*n*=21)	3.2 (3.1–4.16)		
	Pearson correlation coefficient		
	r	*P*	
MC thick	0.89	<0.001 HS	
LC thick	0.81	<0.001 HS	

Dkk: Dickkopf-1, K-L: Kellgren and Lawrence, LC: Lateral condyle, MC: Medial condyle, HS: Highly significant, NS: Not significant, MW: Mann–Whitney *U*-test

Theologis *et al*.[8] demonstrated that blood Dkk-1 levels in OA patients did not differ substantially from those in control subjects ($P = 0.630$). The disparity in results could be attributed to ethnic differences, concomitant diseases, diurnal and activity-related fluctuations in plasma Dkk-1, and differences in the severity and presentation of OA disease.

Our findings are consistent with those of de Miguel Mendieta *et al*.,[21] who discovered a strong positive connection between higher K-L grades and VAS pain levels. In advanced radiographic knee OA (K-L grade 4), sonographic findings of the knee joint revealed a high level of synovial effusion as well as a significant loss of the femoral hyaline articular cartilage thickness in comparison to the other K-L grades. Hall *et al*.[22] reported a correlation between US findings of joint effusion and higher radiological grades, which is in line with our findings.

In the current study, serum Dkk-1 levels were considerably higher in patients with early-stage radiographic knee OA (K-L grade 2) as opposed to those with advanced knee OA (K-L grade 4), which is consistent with previous research.[2,17,23] Consistent with our results, Honsawek *et al*.[2] found an adverse relationship between the progression of knee OA and the levels of circulating Dkk-1. Furthermore, Lane *et al*.[23] found that higher serum levels of Dkk-1 seemed to be related to a slower course of radiographic OA of the hip in older women.

On the other hand, Theologis *et al*.[8] found a direct correlation between Dkk-1 levels in the blood and the degree of severity of knee OA, which contradicts our findings. They observed that, compared to individuals with end-stage knee OA, those with early-stage knee OA (K-L grades 2 and 3) had lower circulating Dkk-1 levels.

Dkk-1 has been shown to be a significant negative modulator of osteoblast development and to impede new bone growth and subchondral bone remodeling.[24,25] Leijten *et al*.,[26] for example, claim that Dkk-1 acts as an innate suppressor of mechanisms that promote the development of OA. Therefore, elevated levels of Dkk-1 in the bloodstream may indicate that an individual has mild-to-moderate OA of the knee and that Dkk-1 has the ability to inhibit bone remodeling around the osteoarthritic joint. The idea that Dkk-1 might be able to stop the loss of articular cartilage is fascinating.

In the current study, it was found that individuals with sonographic gray-scale findings of synovial knee effusion and decreased femoral articular cartilage thickness were correlated with decreased serum levels of Dkk-1. These findings could be explained by previous research that found a relationship between circulatory Dkk-1 levels and the pathophysiology of joint inflammation and the resulting joint degradation in knee OA.[19,27,28]

There are several limitations to our study. The first limitation is that our sample contains a small number of OA patients. To validate our findings, a larger study will be required. Another constraint is the lack of Dkk-1 synovial fluid samples. Moreover, it remains unknown whether bodily activities might affect the blood levels of DKK-1. Daytime and activity-related changes in blood Dkk-1 may thus necessitate more research. Finally, further study is required on other Wnt antagonists, including frizzled protein.

Conclusion

The current study demonstrated a notable increase in circulating Dkk-1 blood levels as well as a strong adverse relationship with the radiological progression in individuals with primary OA of the knee. Reduced circulating Dkk-1 levels were found to be linked to ultrasonographic evidence of synovitis and decreased femoral articular cartilage thickness. The results of this study suggest that circulating Dkk-1 might be employed to serve as a predictive measure determining the degree of progression of primary knee OA. To provide effective therapeutic options to halt the progression of OA, further studies should be conducted to ascertain the role of Dkk-1 in the pathogenesis of chronic degenerative joint disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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