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Plasma and synovial fluid sclerostin are inversely associated with radiographic severity of knee osteoarthritis

Thomas Mabey [a], Sittisak Honsawek [a,b,*], Aree Tanavalee [b], Vajara Wilairatana [b], Pongsak Yuktanandana [b], Natthaphon Saetan [a], Dong Zhan [a]

[a] Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand
[b] Department of Orthopaedics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand

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ABSTRACT

Objective: The purpose of this study was to analyze sclerostin in plasma and synovial fluid of knee osteoarthritis (OA) patients and to investigate the association between sclerostin levels and radiographic severity.

Design and methods: A total of 190 subjects (95 knee OA patients and 95 healthy controls) were recruited in the present study. Sclerostin levels in plasma and synovial fluid were assessed using an enzyme-linked immunosorbent assay. OA grading was performed using the Kellgren–Lawrence classification.

Results: Plasma sclerostin levels were significantly lower in OA patients than in healthy controls ($P = 0.004$). Additionally, sclerostin levels in plasma were significantly higher with respect to paired synovial fluid ($P < 0.001$). Moreover, sclerostin levels in plasma and synovial fluid demonstrated a significant inverse correlation with the radiographic severity of knee OA ($r = -0.464$, $P < 0.001$ and $r = -0.592$, $P < 0.001$, respectively). Subsequent analysis revealed that there was a positive correlation between plasma and synovial sclerostin levels ($r = 0.657$, $P < 0.001$).

Conclusions: Sclerostin was significantly lower in OA plasma samples when compared with healthy controls. Plasma and synovial fluid sclerostin levels were inversely associated with the radiographic severity of knee OA. Therefore, sclerostin may be utilized as a biochemical marker for reflecting disease severity in primary knee OA.

Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease which particularly affects weight bearing joints, predominantly the hips and knees, with which pain, joint swelling, reduced motion, and stiffness are commonly associated. The pathophysiology of OA is contributed to by three main joint tissue types; the synovium, cartilage, and subchondral bone. Articular cartilage destruction with joint space narrowing, osteophyte formation, subchondral bone sclerosis, and synovitis are characteristics of osteoarthritis [1]. The exact aetiology of OA remains obscure but there are a number of known associated risk factors including age, obesity, alterations in joint mechanical stability, genetic predisposition, and previous joint trauma [2]. Nevertheless, loss of articular cartilage, subchondral sclerosis, and bone remodelling have been known to play important roles in OA development.

Wnt/β-catenin signalling has a substantial role in bone and cartilage homeostasis in the adult skeleton, and has been implicated in the process of cartilage degradation in osteoarthritis [3]. Sclerostin, encoded by the *SOST* gene, is an exclusively osteocyte-derived protein that contains a signal peptide for secretion and a cysteine-knot motif [4]. The amino acid sequence of sclerostin has a 20–24% similarity with a specific subfamily of cysteine knot-containing proteins termed the DAN (differential screening-selected gene aberrative in neuroblastoma) family of secreted proteoglycans [5]. Sclerostin is secreted as a monomer in contrast to many other cysteine-knot proteins which form disulfide-linked homodimers [6]. Inactivating mutations in the *SOST* gene can cause sclerosteosis and van Buchem disease which are bone dysplasia disorders characterized by progressive skeletal overgrowth [7–9]. Sclerostin is expressed by terminally differentiated cells embedded in mineralized matrix including osteocytes and hypertrophic chondrocytes [10,11]. Its downregulation in osteocytes by physical loading of bone contributes to the mechanical sensor function of osteocytes and the subsequent increase in bone growth [12].

The negative regulatory actions of sclerostin occur through the canonical Wnt/β-catenin signalling pathway by binding specifically to low density lipoprotein-related protein 5 and 6 (LRP5/6) and inhibiting their association with Frizzled receptors [13,14]. This binding inhibits the pathway which would normally lead to, among other outcomes, bone formation and can subsequently impact on osteogenesis. Sclerostin has also been shown to be produced in interleukin (IL)-1α stimulated

* Corresponding author at: Department of Biochemistry and Orthopaedics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, 1873 Rama IV road, Patumwan, Bangkok 10330, Thailand. Fax: +66 2 256 4482.
E-mail address: Sittisak.H@chula.ac.th (S. Honsawek).

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chondrocytes within joint cartilage. This was found to be potentially beneficial in protecting against cartilage degradation [15]. In addition, decreased sclerostin expression of osteocytes is associated with increased cortical bone density in hip OA, and sclerostin has previously been shown to be expressed by chondrocytes in mineralized cartilage, indicating a potential role for sclerostin in OA pathogenesis [3].

To our knowledge, no previous study has examined sclerostin with respect to its relationship with radiographic severity in primary knee osteoarthritis. Thus, the objectives of this study were to compare sclerostin levels in plasma and synovial fluid from OA patients and healthy controls, and additionally to investigate the association between plasma and synovial fluid sclerostin levels and radiographic severity in primary knee OA.

Materials and methods

Study subjects

The present study was conducted in agreement with the guidelines of the Declaration of Helsinki, and written informed consent was obtained from all patients and healthy volunteers prior to their participation in the study. This study was approved by the Institutional Review Board on Human Research of the Faculty of Medicine, Chulalongkorn University. The sample size was designed according to the standardized effect size of 0.7, using Student's *t*-test to compare means of continuous variables, a statistical power of 0.8, and a *P*-value of 0.05. Therefore, at least 35 subjects were required in each group.

Ninety-five patients (79 females and 16 males) were diagnosed with primary knee osteoarthritis according to the criteria of the American College of Rheumatology, and 95 healthy volunteers with no clinical and radiological evidence of OA (77 females and 18 males) were enrolled in the present study. All patients were randomly selected and scheduled to undergo diagnostic or therapeutic arthroscopy or total knee arthroplasty in our hospital between January 2009 and August 2011. Clinical data were carefully reviewed to exclude any forms of secondary OA and inflammatory joint diseases. No participant had underlying diseases such as diabetes, advanced liver or renal diseases, histories of medication interfering with bone metabolism (such as corticosteroids or bisphosphonates), other forms of arthritis, cancer or other chronic inflammatory diseases.

Knee radiography was taken when each participant was standing on both legs with fully extended knees and the X-ray beam was centred at the level of the joint. Assessment of radiographic severity was performed using the Kellgren and Lawrence (KL) grading system [16]. Depending on changes observed in conventional weight-bearing anteroposterior radiographs of the affected knee in extension, osteoarthritis was divided into 5 grades (0 to 4): grade 0 (normal findings), no X-ray changes; grade 1 (questionable), doubtful narrowing of joint space and possible osteophyte lipping; grade 2 (mild), definite osteophytes and possible joint space narrowing; grade 3 (moderate), multiple moderate osteophytes, definite narrowing of joint space, bone sclerosis and possible deformity of bone contour; and grade 4 (severe), large osteophytes, marked joint space narrowing, severe sclerosis, and deformity of bone contour. OA patients were defined as having radiographic knee OA of KL grade ≥ 2 in at least 1 knee. Controls were defined as having neither radiographic hip OA nor knee OA, as indicated by KL grades of 0 for both hips and both knees. The grading scale used for analysis was the one found higher upon comparison between both knees.

Laboratory methods

Following a 12-h overnight fast, venous blood samples were collected into ethylenediamine tetraacetic acid (EDTA) tubes, centrifuged, and stored immediately at −80 °C until analysis. Synovial fluid was aspirated from the affected knee of OA patients using sterile knee puncture just prior to surgery when the arthroscopy or total knee arthroplasty was performed. The specimen was then centrifuged to remove cells and joint debris and then stored at −80 °C for further measurement.

Plasma and synovial fluid sclerostin levels were measured using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) development kit (R&D Systems, Minneapolis, MN, USA). According to the manufacturer's instructions, recombinant human sclerostin standards, plasma, and synovial fluid samples were pipetted into each well, which was pre-coated with mouse monoclonal antibody specific for sclerostin. After incubating for 2 h at room temperature, every well was washed thoroughly four times with washing buffer. Then, a horseradish peroxidase-conjugated polyclonal antibody specific for sclerostin was added to each well and incubated for a further 2 h at room temperature. After four washes, substrate solution was pipetted into the wells and then the microplate was incubated for 30 min at room temperature with protection from light. Finally, the reaction was stopped by the stop solution and the colour intensity was measured with an automated microplate reader at 450 nm. The amount of colour generated is directly proportional to the amount of sclerostin in the sample. Sclerostin concentration was determined by a standard optical density–concentration curve. Twofold serial dilutions of recombinant human sclerostin with a concentration of 31.3–2000 pg/mL were used as standards. The intra- and inter-assay coefficients of variation (CVs) were 1.8–2.1% and 8.2–10.8%, respectively. The sensitivity of this assay was 3.8 pg/mL.

Statistical analysis

Statistical analysis was carried out using the statistical package for social sciences (SPSS) software, version 16.0 for Windows. Demographic data between patients and controls were compared by Chi-square tests and unpaired Student's *t*-tests, where appropriate. Comparisons between the groups were performed using one-way analysis of variance (ANOVA) with Tukey post hoc test if ANOVA showed significance. Pearson's correlation coefficient (r) was employed to determine correlations between plasma and synovial fluid sclerostin and clinical characteristics. Data were expressed as a mean ± standard error of the mean. *P*-values < 0.05 were considered to be statistically significant for differences and correlations.

Results

Ninety-five OA patients, aged 49–84 years, and 95 controls, aged 50–80 years were enrolled in the present study. The baseline clinical characteristics of the subjects are displayed in Table 1. There were no statistically significant differences in the ages or gender ratios (female/male) between OA patients and healthy controls. As shown in Fig. 1, plasma sclerostin levels were significantly lower in OA patients than in healthy controls (920.7 ± 62.6 pg/mL vs. 1177.8 ± 72.3 pg/mL, $P = 0.004$). Sclerostin concentrations in synovial fluid of OA patients were nearly twofold lower than in paired plasma samples (526.8 ± 51.3 pg/mL vs. 920.7 ± 62.6 pg/mL, $P < 0.001$). Plasma sclerostin levels exhibited a positive correlation with synovial fluid sclerostin levels ($r = 0.657$, $P < 0.001$) (Fig. 2).

In order to reduce the confounding effect of age, using the mean age of 70 years, the study population was divided into a middle-aged (those <70 years of age, n = 51) and an elderly (those ≥70 years of age, n =

Table 1
Baseline clinical characteristics of knee OA patients and controls.

	OA patients	Controls	*P*
Number	95	95	
Age (years)	69.5 ± 0.8	68.2 ± 0.7	0.2
Gender (female/male)	79/16	77/18	0.5

OA = Osteoarthritis.

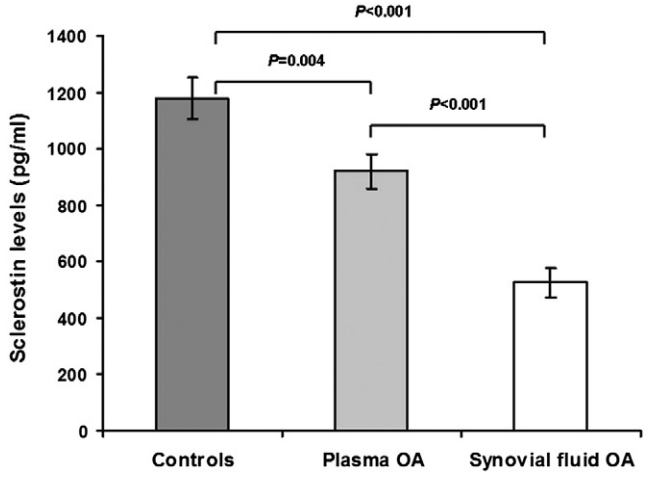

Fig. 1. Sclerostin levels in plasma and synovial fluid of OA patients and healthy controls.

44) subgroup. Although the elderly patients had higher plasma sclerostin than the middle-aged patients, the difference was not statistically significant (923.0 ± 78.8 pg/mL vs. 918.7 ± 95.6 pg/mL, $P = 0.5$). There was no significant correlation between plasma sclerostin levels and age in controls or in knee OA patients ($P = 0.2$). No significant differences in plasma sclerostin levels were found between genders in controls or in knee OA patients ($P = 0.4$).

According to the radiographic KL classification, OA patients were divided into 3 subgroups in relation to OA grading (KL grade 2: 29; KL grade 3: 31; KL grade 4: 35). The synovial fluid and plasma levels of sclerostin in OA patients with different KL subgroups are present in Table 2. Knee OA patients with higher radiographic severity had significantly lower sclerostin levels in both plasma and synovial fluid ($P < 0.001$).

Subsequently, the relationships between plasma and synovial fluid levels of sclerostin and the disease severity of knee OA were evaluated. The plasma levels of sclerostin were negatively correlated with the knee OA severity ($r = -0.464$, $P < 0.001$) (Fig. 3). Further analysis revealed that synovial fluid sclerostin levels of OA patients were also inversely correlated with the radiographic severity ($r = -0.592$, $P < 0.001$) (Fig. 4).

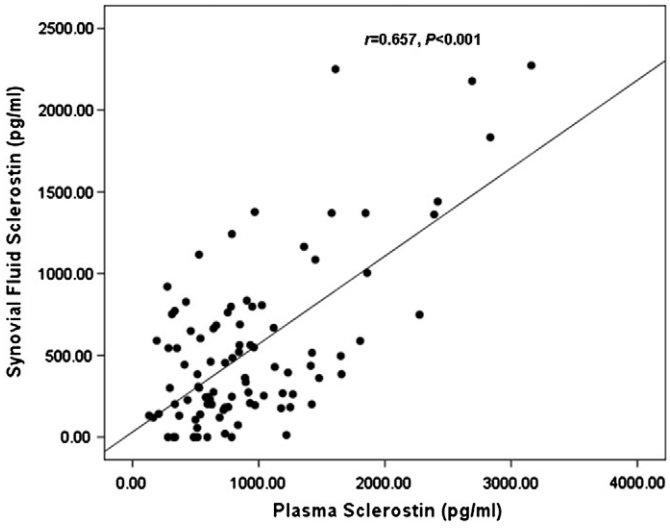

Fig. 2. Positive correlation between plasma and synovial fluid sclerostin levels in OA patients ($r = 0.657$, $P < 0.001$).

Discussion

The Wnt signalling pathway influences bone formation through effects on osteoblast number, maturation, and progenitor differentiation and these actions are opposed by various intracellular and secreted factors [17]. Wnt signalling is modulated by soluble antagonists including dickkopf-1 (Dkk-1), secreted frizzled-related proteins (sFRPs), and sclerostin [18]. In adult cartilage, enhanced Wnt/β-catenin activates tissue breakdown rather than formation [19]. Stimulation of constitutive β-catenin activity in mouse chondrocytes results in progressive cartilage destruction and increased subchondral bone sclerosis [20]. Recently, circulating Dkk-1 levels negatively correlate with the radiographic severity of knee OA patients [21]. Therefore, elevated β-catenin activity may be a common mechanism in the excess bone formation and overlying cartilage loss in OA.

It has been previously reported that circulating sclerostin is present in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) [22,23]. However, to the best of our knowledge, the relationship between circulating and synovial fluid levels of sclerostin and disease severity has never been investigated in OA patients, and data on the association of sclerostin levels in plasma and synovial fluid have as yet not been documented in the literature. The current study has been the first to demonstrate that sclerostin was detected in both plasma and synovial fluid obtained from patients with primary knee OA. Plasma sclerostin levels in OA patients were significantly lower than those in healthy controls. In addition, synovial fluid sclerostin concentrations in OA patients were markedly decreased compared to paired plasma sclerostin. Moreover, both plasma and synovial fluid sclerostin levels were inversely correlated with the radiographic severity in knee OA patients.

In the present study, it appeared that plasma sclerostin was significantly reduced in patients with primary knee OA compared to the controls. Our results suggest that there is a decreased systemic production of sclerostin in knee OA. It should be noted that sclerostin levels in synovial fluid were significantly lower than those observed in paired plasma samples. This result was in accord with our previous studies of Dkk-1, adiponectin, and interferon-γ inducible protein-10 in primary knee OA [21,24,25]. Recently, Pilichou et al. showed that the ratio of receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) was decreased in synovial fluid of OA patients compared with the corresponding blood samples [26]. They also revealed that circulating RANKL and RANKL/OPG ratio correlated with the severity in knee OA. In contrast with these findings, Kenanidis and coworkers demonstrated no correlation between circulating RANKL and OPG and the radiographic severity of hip and knee OA [27].

The reason for lower sclerostin levels in synovial fluid may be attributed to the limited transport of sclerostin across the synovial membrane barrier. The source of sclerostin could originate from the local tissues (inflamed synovium, cartilage, and subchondral bone) and extra-articular tissues. Previous studies have shown that sclerostin was expressed in articular cartilage chondrocytes and subchondral bone osteoblasts in OA knees [15,23,28,29]. Alternatively, it is possibly due to the increased sclerostin clearance, which exceeded its production. Sclerostin levels in plasma and synovial fluid were measured in a well-defined knee OA population at every stage of disease, and were significantly lower in end-stage knee OA patients compared with early OA patients. This observation indicates a significant reduction in the systemic and local expression of sclerostin in patients with advanced knee OA. The mechanisms of sclerostin reduction in the circulation and synovial fluid of OA patients remain to be elucidated further.

In agreement with our results, Appel et al. reported serum levels of sclerostin to be significantly lower in AS patients in comparison to healthy controls [23]. In a subgroup analysis, the level of sclerostin was significantly higher in patients with no syndesmophyte development than in patients with new syndesmophyte growth. They concluded that low sclerostin levels in AS were found to be associated with syndesmophyte formation and radiographic progression and might be

Table 2
Plasma and synovial fluid sclerostin levels in knee osteoarthritis patients. Data are expressed as mean and SEM. *P*-values for differences among Kellgren and Lawrence subgroups.

	Total	KL grade 2	KL grade 3	KL grade 4	*P*
Number	95	29	31	35	
SF sclerostin (pg/mL)	526.8 ± 51.3	904.6 ± 93.3	558.4 ± 86.0	185.8 ± 32.8	<0.001
Plasma sclerostin (pg/mL)	920.7 ± 62.6	1286.6 ± 111.0	944.8 ± 113.5	596.2 ± 67.8	<0.001

KL = Kellgren and Lawrence.
SF = Synovial fluid.

useful as a biomarker to assess the risk of developing syndesmophytes in AS. Furthermore, sclerostin-positive osteocytes were significantly decreased in lumbar zygapophyseal joints of patients with OA in which bony spurs form [23]. Thus, low sclerostin levels might indicate the susceptibility for osteophyte formation in osteoarthritis. These findings are also in line with those of a previous study by Power et al. [28], in which femoral neck bone samples of hip OA patients were found to have fewer osteocytes when compared with those of postmortem controls. Sclerostin expression in osteocytes was also observed to be decreased. In contrast to our results, Korkosz et al. reported serum levels of sclerostin to be significantly higher in AS patients with high disease activity than in healthy subjects [30]. This contrasts our results where lower sclerostin levels in OA patients were associated with a higher degree of disease severity. The possible explanation of these conflicting results may be ascribed to differences in disease advancement, populations or assays applied, or to incomplete control of confounding variables.

A recent study has illustrated that sclerostin expression was enhanced in the chondrocyte clusters of damaged OA articular cartilage but markedly decreased in the subchondral bone osteocytes of post-traumatic OA [15]. Roudier and colleagues also showed sclerostin expression in human articular chondrocytes, including human OA cartilage [31]. These findings indicate a regulatory role of sclerostin in OA pathogenesis and suggest a dual effect in promoting subchondral bone sclerosis while inhibiting destruction of articular cartilage. Increasing Wnt/β-catenin activity using antibodies to sclerostin may provide potential benefit for treating osteoarthritis.

The potential shortcomings of the present study merit consideration. First, this is a cross-sectional study with a relatively small sample size; such a study cannot establish definite cause-and-effect relationships. It shows some association and is hypothesis generating. The conclusions drawn from our data should be applied with caution to other populations. Insignificant results in age and gender-related plasma levels of sclerostin could be attributable to an inadequate sample size. Therefore, the association should be elucidated in multi-centre prospective longitudinal investigations with larger sample sizes. Second, we did not collect synovial fluid samples from healthy controls due to ethical reasons, which might induce some bias. Third, sclerostin levels were only measured in the plasma and synovial fluid. Further studies examining sclerostin expression in local tissues, in relation to the synovial and circulating sclerostin levels, could provide a more valuable insight into the pathogenic role of sclerostin in OA. Additional limitation is that patients were not screened for other possible sites of OA, such as hand, hip, and/or spinal OA. Moreover, seasonal variation and physical activity have been reported to influence circulating sclerostin levels [32,33]. Therefore, seasonal and activity-related variations in plasma and synovial sclerostin will need to be further investigated. Last, we did not determine functional impairment, pain, and clinical symptoms in these patients. More studies are warranted to determine whether sclerostin correlates with functional impairment (WOMAC or Lequesne score) and pain (visual analogue scale). Insufficient assessment of potential confounders such as age, gender, and medical comorbidities needs to be taken into account.

In conclusion, OA patients have reduced plasma concentrations of sclerostin when compared with healthy controls. Additionally, plasma and synovial fluid sclerostin levels are inversely associated with the radiographic severity in knee OA. These findings supported the hypothesis which portrayed sclerostin as a protective factor in OA. Sclerostin might serve as a possible biochemical marker of knee OA for reflecting the degenerative process of primary knee OA. This study provides evidence for the role of sclerostin in the development and severity of knee OA. Further studies on the sclerostin signalling pathway are necessary to gain insight into the discovery of novel therapeutic agents against osteoarthritis.

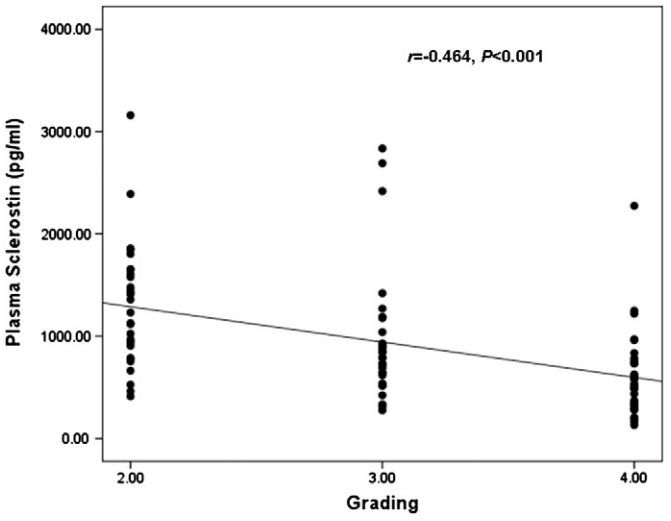

Fig. 3. Negative correlation between plasma sclerostin levels in OA patients and disease severity classified according to Kellgren and Lawrence grading scale ($r = -0.464$, $P < 0.001$).

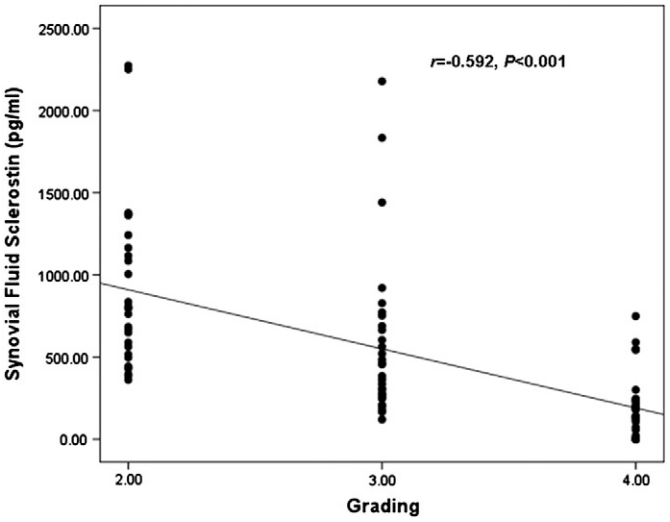

Fig. 4. Negative correlation between synovial fluid sclerostin levels in OA patients and disease severity classified according to Kellgren and Lawrence grading scale ($r = -0.592$, $P < 0.001$).

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