The role of sclerostin in knee osteoarthritis and its relation to disease progression

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Background
Osteoarthritis (OA) is a common joint disease especially in aging population and is characterized by progressive degeneration of articular cartilage, osteophyte formation, and subsequent joint space narrowing. Sclerostin, a protein product of the SOST gene, secreted mainly by osteocytes causes inhibition of Wnt/β-catenin signaling pathway and bone morphogenetic protein, therefore may affect bone formation and bone remodeling in OA.
Aim
The aim was to assess serum sclerostin level in patients with knee osteoarthritis (KOA) and its relation to disease severity.
Patients and methods
A total of 80 participants (50 KOA patients and 30 healthy controls) were recruited in the present study. Sclerostin level in plasma was assessed using an enzyme-linked immunosorbent assay. OA grading was performed using the Kellgren–Lawrence classification. Assessment of physical disability was done by Western Ontario and McMaster universities Arthritis index score and health assessment questionnaire score.
Results
Plasma sclerostin levels were significantly lower in patients with OA than in healthy controls ($P<0.001$). Moreover, serum sclerostin level demonstrated a significant inverse correlation with the physical disability score ($r=-0.506$, $P<0.01$), age ($r=-0.295$, $P<0.01$), disease duration ($P<0.05$), and radiographic severity of KOA ($P<0.001$). By univariate regression analysis, sclerostin was one of the strong negative predictors for severity of OA.
Conclusion
Sclerostin was significantly lower in OA plasma samples when compared with healthy controls. Serum sclerostin level was inversely associated with the physical disability and radiographic severity of KOA. Therefore, sclerostin may be used as a biochemical marker for reflecting disease severity in primary KOA.

Keywords:
health assessment questionnaire score, Kellegren Lawrence score, knee osteoarthritis, osteoarthritis, serum sclerostin, Western Ontario and McMaster universities Arthritis index score

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Introduction

Osteoarthritis (OA) is the most common joint disease worldwide. It is mainly characterized by articular cartilage degeneration, joint capsule hypertrophy, remodeling of subchondral bone, formation of osteophytes, laxity of surrounding ligaments, and synovial inflammation [1]. The exact etiology 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] Knee osteoarthritis (KOA) is a major cause of pain and functional disability among older adult [3].

Sclerostin is a protein encoded by the SOST gene. In humans, it was originally believed to be a nonclassical bone morphogenetic protein antagonist [4]. Its downregulation in osteocytes by physical loading of bone contributes to the mechanical sensor function of osteocytes and the subsequent increase in bone growth [5]. The negative regulatory actions of sclerostin occur through the canonical Wnt/β-catenin signaling pathway by binding specifically to low-density lipoprotein-related protein 5 and 6 (LRP5/6) and inhibiting their association with Frizzled receptors [6]. Microarray analysis of Wnt pathway also suggests the possible involvement of this pathway in altered bone remodeling in OA. Inhibition of Wnt

signaling and bone morphogenetic protein by sclerostin therefore may affect bone formation and bone remodeling in OA. Taken together, all these data demonstrate that the anti-anabolic action and catabolic action of sclerostin may be a potential mechanism of subchondral bone changes in OA [7]. Sclerostin has also been detected to be produced in interleukin-1α-stimulated chondrocytes within the joint cartilage. This was found to be potentially beneficial in protecting against cartilage degradation [8].

Aim

The present study aimed at assessment of the serum level of sclerostin in a cohort of patients with KOA and its relation to degree of structural damage and function impairment.

Patients and methods

Study design

This is a cross-sectional observational case–control study.

Clinical evaluation

A total of 50 patients with primary knee OA were included in this study. All patients have fulfilled the 2016 revised criteria of American College of Rheumatology for diagnosis of knee OA [9]. In addition, 30 age-matched and sex-matched healthy volunteers served as a control group for serum sclerostin level. They were randomly recruited from the Ain Shams University Hospital, Internal Medicine Department and Rheumatology Outpatient Clinic between June 2017 and June 2018. The study was approved by the Local Research Ethical Committee of Ain Shams University and conforms to the provisions of the Declaration of Helsinki in 1995. All participants gave written informed consent to be included after explaining the nature of the study.

Exclusion criteria

The following were the exclusion criteria:

(1) Secondary OA.
(2) Inflammatory joint diseases.
(3) Patients with histories of medication interfering with bone metabolism, such as corticosteroids or bisphosphonates.

Clinical assessment

Detailed history taking and thorough clinical examination was performed with special emphasis on knee examination (knee stiffness, swelling, locking, effusion and tenderness). BMI was calculated by the following equation: BMI=weight/height (m^2) with weight in kilograms and height in meters. Assessment of physical disability was by health assessment questionnaire (HAQ) [10] and Western Ontario and McMaster universities Arthritis index (WOMAC) Questionnaire [11].

Laboratory assessment

Laboratory investigations included the following:

(1) Complete blood count, erythrocyte sedimentation rate, and C-reactive protein.
(2) Measurement of serum sclerostin level: it was done by enzyme-linked immunosorbent assay method (ELISA) using human sclerostin (SOST) ELISA Kit (PEOBIOTECH GmbH-Am klopferspitz 19-82152, Planegg, Germany).

Radiological assessment

Knee radiography was taken when each participant was standing on both legs with fully extended knees, and the radiographic beam was centered at the level of the joint. Radiological assessment of severity of radiological joint damage was done using Kellgren and Lawrence system (narrowing and osteophytes formation) [12].

Statistical methods

IBM SPSS16 Statistics (IBM Company, New York City, USA) was used for data analysis. Data were expressed as mean±SD for quantitative parametric measures in addition to median percentiles for quantitative nonparametric measures, and both number and percentage were used for categorized data.

The following tests were done:

(1) Mann–Whitney test was used to compare two independent groups.
(2) The relation between more than two studied groups regarding quantitative data with nonparametric distribution was done by using Kruskal–Wallis test.
(3) Ranked Spearman's correlation test was done to study the possible association between each two variables among each group for nonparametric data.

The confidence interval was set to 95%, and the margin of error accepted was set to 5%. The probability of error at 0.05 was considered significant, whereas at 0.01 and 0.001 as highly significant.

Results

The present study included 50 patients with OA, comprising 43 (86%) females and seven (14%) males, with an age ranging from 40 to 73 years (51.9±8.24 years). Their BM) ranged from 25.25 to 39.1 kg/m^2 (31.59±3.61). The general features and clinical manifestations, laboratory findings, radiographic findings, and functional disability scores of the studied patients with OA are displayed in Table 1.

Median serum sclerostin level was highly significantly decreased in the patient group in comparison with the controls group (8.75 and 14, respectively) (P=0.000). Serum sclerostin level was significantly higher in patients with low HAQ score and those who had grade 1 Kellgren and Lawrence score than those with higher disability and radiological damage scores (P<0.05), whereas its level was significantly decreased in patients who had radiological evidence of joint space narrowing (P<0.01), marginal osteophytes (P<0.05), and knee deformity (P<0.05) than those who did not have the same radiographic findings (Table 2).

Table 1 Clinical characteristics and laboratory findings of the studied patients with osteoarthritis

	Patients with OA (n=50)
Variables	Mean±SD or n (range or %) or n (%)
Age (years)	51.90±8.24
Disease duration	4.00 (2–7) (1–22)
BMI (kg/m^2)	31.59±3.61
Sex	
Females	43 (86)
Males	7 (14)
Knee pain	50 (100)
Morning stiffness <30 min	50 (100)
Limitation of movement	50 (100)
Tenderness	50 (100)
Crepitus	49 (98)
ESR (mm/h)	28.04±9.19 (8–40)
CRP titer (mg/l)	3.60 (6–12)
Serum sclerostin level [median (IQR)/range]	8.75 (4.5–14) (1.8–95)
HAQ score	
Mild	19 (38)
Moderate	26 (52)
Severe	5 (10)
Total WOMAC score	59.26±15.76 (22–82.2)
Radiographic findings	
Joint space narrowing	47 (94)
Marginal osteophyte	48 (96)
Deformity	5 (10)
Kellgren and Lawrence score	
Grade 1	4 (8)
Grade 2	19 (38)
Grade 3	22 (44)
Grade 4	5 (10)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire.

Mean serum sclerostin level showed a statistically significant negative correlation with both age (P<0.05) and disease duration (P<0.01), but it had no statistically significant correlation regarding BMI among the studied patients with OA (P>0.05). There was a statistically highly significant negative correlation between mean serum sclerostin level and HAQ score (r=−0.506, P=0.000), WOMAC score (r=−0.574, P=0.000), and subscales of WOMAC (total pain score, total stiffness scores, and total physical function score, with r=−0.389, P=0.005; (r=−−0.422, P=0.002; and r=−0.464, P=0.001, respectively) (Table 3).

On assessment of severity of radiological joint damage of OA by Kellegren–Lawrence score, the results showed that there was a highly significant relation between mean serum sclerostin level and the increase of Kellegren–Lawrence score (P<0.001) (Fig. 1). By univariate linear regression analysis for predictors of severity of radiological joint damage, HAQ score, BMI, mean serum sclerostin level (P<0.05), and erythrocyte sedimentation rate (P<0.01) were independent predictors for severity of radiological damage of OA (Table 4).

Receiver operating characteristic curve showed that the best cutoff value of serum sclerostin to detect severity of radiological joint damage of OA was less than 7.7, with diagnostic sensitivity of 78.57% and specificity of 68.18% (Fig. 2).

Discussion

OA is a chronic disorder characterized by cartilage loss, bone remodeling, joint deformity, and synovial inflammation. It is the most common joint disease in humans [13,14] The knee is commonly affected; it is frequent (50%) among the population aged above 60 years, and peaks (80%) at 75 years [15]. The most often affected compartments are the patellofemoral and medial tibiofemoral. Severe bone and cartilage loss leads to instability and varus (bow) deformity. Instability and 'giving way' of a knee may be exacerbated by quadriceps weakness. It is considered to be a natural consequence of aging [16].

In the present study, the mean age of the studied patients included in current study was 51.9±8.24 years, and most patients were females (86%). This

Table 2 Comparison between serum sclerostin level and grades of physical disability, radiological damage scores, and presence or absence of radiographic findings among studied patients with osteoarthritis

Variables	Mean serum sclerostin level		Kruskal–Wallis test/Mann–Whitney test	*P* value
	Median (IQR)	Range		
Mean serum sclerostin level				
Patients	8.75 (4.5–14)	(1.8–95)		
Controls	14(12–22)	(11–32)		*0.000*
HAQ score				
Mild	12.0 (8–44)	1.8–95		
Moderate	6.85 (4–12)	2.2–95	6.961	<0.05
Severe	4.1 (4–8)	3–10		
Kellgren and Lawrence score				
Grade 1	74.5 (28.9–97.5)	3.9–100		
Grade 2	10.1 (7–15)	4–45		
Grade 3	5.1 (3.9–11)	1.8–44	8.044	<0.05
Grade 4	8 (3–8.5)	2.9–12		
Radiographic findings				
Joint space narrowing				
Yes	8 (4.1–13)	1.8–95	–2.697	0.007
No	54 (45–95)	45–95		
Marginal osteophyte				
Yes	8.25 (4.3–13)	1.8–95	–2.179	<0.05
No	70 (45–95)	45–95		
Deformity				
Yes	7 (3.3–7)	3–7.7	–2.087	<0.05
No	10 (4.6–15)	1.8–95		

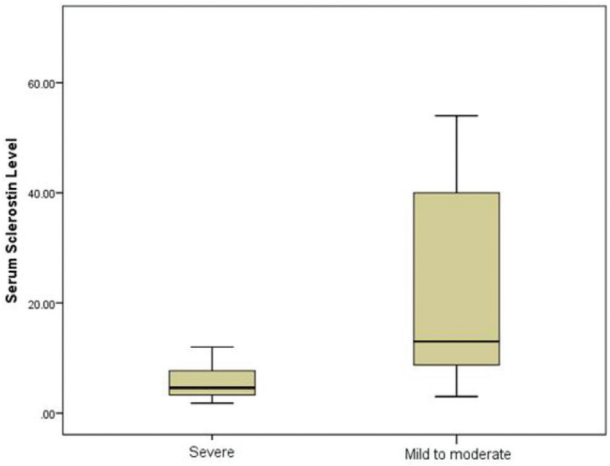
IQR, interquartile range; HAQ, health assessment questionnaire.

Table 3 Correlation between a mean serum sclerostin level and age, disease duration, and physical disability scores among studied patients with osteoarthritis

Variables	Mean serum sclerostin level	
	r	*P* value
Age	–0.295	0.038
Disease duration	–0.420	0.002
HAQ score	–0.506**	0.000
Total WOMAC score %	–0.574**	0.000
Total pain score	–0.389**	0.005
Total stiffness scores	–0.422**	0.002
Total physical function score	–0.464**	0.001

HAQ, health assessment questionnaire; WOMAC, Western Ontario and McMaster universities Arthritis index. $P>0.05$, nonsignificant. $P<0.05$, significant. $P<0.01$, highly significant.

Figure 1



Relation between the severities of osteoarthritis stage by Kellegren-Lawrence score and serum sclerostin level among studied patients with osteoarthritis.

finding was in agreement with other studies which reported an increased frequency of OA with age and in females [17–20]. Most of the studied patients with OA (74%) were obese, with high BMI ranged from 25.25 to 39.1 kg/m^2 with mean 31.59±3.61 kg/m^2. This result is similar to the results of previous studies [21–23] which suggested that high BMI was significantly associated with knee OA. Moreover, it was reported that an increase of 5 kg/m^2 in BMI had been associated with 32% increase in the probability of knee OA, which suggested the shared pathogenetic role for metabolic factors with knee OA [24]. All patients (100%) complained of knee pain with atypical morning stiffness less than 30 min, and this finding was in agreement with the results of other studies [25–28].

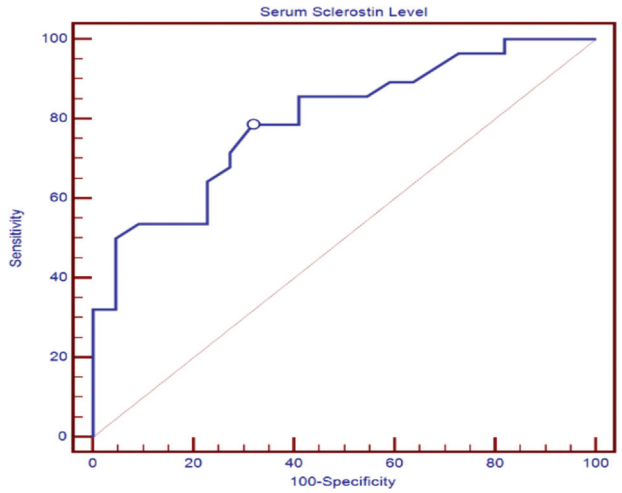
Sclerostin has previously been shown to be expressed by chondrocytes in mineralized cartilage, indicating a potential role for sclerostin in OA pathogenesis [29]. A previous study has illustrated that sclerostin expression was enhanced in the chondrocyte clusters

Table 4 Univariate linear regression for predictors of severity of radiological joint damage by Kellegren and Lawrence score among studied patients with osteoarthritis

Variables	Unstandardized coefficients		Standardized coefficients	Logistic regression test		
	B	SE	*β*		Significance	
Age	0.000	0.011	−0.002	−0.010	0.992	NS
Disease duration	−0.002	0.035	−0.007	−0.046	0.963	NS
BMI	−0.006	0.031	0.328	2.197	<0.05	S
Erythrocyte sedimentation rate	0.026	0.012	0.305	2.220	<0.05	S
C-reactive protein titer	0.034	0.030	0.158	1.109	0.273	NS
Health assessment questionnaire score	0.723	0.231	0.411	3.126	0.003	HS
Western Ontario and McMaster Universities Osteoarthritis Index score percentage	0.008	0.007	0.164	1.154	0.254	NS
Mean serum sclerostin level	−0.010	0.005	−0.273	−2.368	<0.05	S

HS, highly significanct; S, significant.

Figure 2



Receiver operating characteristic curve of serum sclerostin level as an independent predictor for radiological joint damage severity in osteoarthritis.

of damaged OA articular cartilage but markedly decreased in the subchondral bone osteocytes of post-traumatic OA [8]. In the current study, the mean serum sclerostin level among studied patients with OA was decreased significantly; this finding is in agreement with previous studies [30,31]. Roudier and colleagues also showed sclerostin expression in human articular chondrocytes, including human OA cartilage [32]. The negative regulatory actions of sclerostin occur through the canonical Wnt/β-catenin signaling pathway by binding specifically to low-density lipoprotein-related protein 5 and 6 (LRP5/6) and inhibiting their association with Frizzled receptors. This binding inhibits the pathway which would normally lead to bone formation and can subsequently affect osteogenesis. Sclerostin has also been shown to be produced in interleukin-1α-stimulated chondrocytes within joint cartilage. This was found to be potentially beneficial in protecting against cartilage degradation; in addition, decreased sclerostin expression by osteocytes is associated with increased cortical bone density in hip OA [29]. These findings may give a new insight about the 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 OA.

In the present study, we found that the mean serum sclerostin level decreased among studied patients with OA with high BMI. This result agreed with the study by Armamento-Villareal *et al.* [33], who found that serum sclerostin significantly increased in patients with low BMI. This result suggests that the reduction in skeletal stress associated with weight loss leads to increase in sclerostin production by mechanostat in bone tissues.

Moreover, in the present study, there was a significant negative correlation between the presence of radiological findings of OA (joint space narrowing, osteophytes formation, and deformities) and mean serum sclerostin level. The same significant negative correlation was found between sclerostin and the grades of severity of radiologic damage assessed by Kellgren and Lawrence score. This was in agreement with a study done by Bouaziz *et al.* [34], who found that knee OA mice with low sclerostin had a high OA score and stated that loss of sclerostin promotes OA in mice via β-catenin-dependent and –independent Wnt pathways. This was also in agreement with a study done by Wu *et al.* [19], who found reduction of sclerostin levels with the increase in pathological stage of OA, and it negatively correlated with the severity of degeneration. This finding may suggest

that the Wnt signaling pathway influences bone formation through effects on osteoblast number, maturation, and progenitor differentiation, and these actions are opposed by various intracellular and secreted factors [35].

Moreover, the results showed a negative correlation between mean serum sclerostin and HAQ disability score. Unfortunately, to the best of our knowledge, the relationship between circulating levels of sclerostin and the functional impairment (WOMAC or HAQ disability score) has never been investigated in patients with OA, and data on the association of sclerostin levels in plasma and functional impairment have not yet been documented in the literature. Comparison between the mean serum sclerostin level and different radiographic findings (joint space narrowing, marginal osteophytes, and deformities) showed that the patients who had these findings had a lower serum sclerostin level than those who did not have the same clinical findings, which may support that decrease in serum sclerostin level increases the severity of OA, which is clinically reflected with various clinical and radiological manifestations. This explains the role of sclerostin in pathogenesis of OA, as mechanical loading is known to influence sclerostin expression, which affects signal transduction in articular cartilage [36]. On assessment of predictors of severity of knee OA among studied patients, sclerostin was one of the strong negative predictor for severity of OA, which supports its role in pathogenesis and progression of OA, so its early measurement in patients of OA is a step for early diagnosis and better management. Moreover, a strong positive predictor for severity of knee OA was high BMI (obesity). This is in agreement with Keng *et al.* [23], who reported a trend toward significance of BMI with cartilage damage severity; participants with abnormal current BMI greater than or equal to 25 had a threefold increased odds of cartilage damage greater than or equal to 2, compared with those with normal BMI.In conclusion, patients with OA have lower plasma concentrations of sclerostin when compared with healthy controls, especially with older age and longer disease duration. Additionally, plasma sclerostin levels are inversely associated with the radiographic severity and the degree of functional impairment in knee OA. These findings may support the hypothesis, which portrayed sclerostin as a protective factor in OA. Sclerostin might serve as a possible prognostic biochemical marker of knee OA.

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. Second limitation of the study 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 [29,33]. Therefore, seasonal and activity-related variations in plasma and synovial sclerostin will need further investigation

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Conflicts of interest
There are no conflicts of interest.

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