Sclerostin level in rheumatoid arthritis patients and its relationship to disease severity and bone mineral density

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Received 6 February 2019
Accepted 15 April 2019

Egyptian Journal of Obesity, Diabetes and Endocrinology 2018, 4:82–89

Background
Bone loss in rheumatoid arthritis is caused by increased bone resorption without increasing bone formation. The Wnt pathway is important in the control of bone formation through the regulation of osteoblast activity. Sclerostin is an important regulator of the Wnt pathway by blocking Wnt binding to its receptor and thereby , inhibiting bone formation.
Aim Of The Work
was to correlate the relation between level of serum sclerostin and bone mineral density with disease severity in rheumatoid arthritis patients.
Subjects
The study was conducted on 50 subjects divided into two groups: Group I : Thirty patients of rheumatoid arthritis subjects diagnosed according to 2010 ACR / EULAR diagnostic criteria. Group II : Twenty persons as a control group.
Methods
All patients were subjected to ; thorough medical history taking, DAS -28, disability Index, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF, antinuclear antibody (ANA), Anti-CCP Antibodies, Human Sclerostin levels using ELISA technique, Plain X- ray on both hands and feets, U/S on both hands, and (DEXA) scan.
Results
There was a statistical significant difference between the two studied groups regarding the age, gender, sclerostin level, and DAS-28 ($P>0.05$).
Conclusion
Most of patients were under treatment with disease modifying anti-rheumatic drugs (DMARDs) as methotrexate, fracture risk was not assessed, and measurements for renal function were not measured. However, it is possible that circulating sclerostin levels may not reflect changes of sclerostin at a local level. Despite the many questions that remain, pre-clinical studies and clinical trial results would imply that sclerostin antibodies will emerge as a dominant first- line treatment in the management of osteoporosis.

Keywords:
bone mineral density, rheumatoid arthritis, sclerostin, wnt pathway

Egypt J Obes Diabetes Endocrinol 4:82–89

2356-8062

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease affecting ~1% of the population worldwide [1]. It is characterized by chronic and symmetric inflammation of the synovial joints, leading to joint destruction, chronic joint pain, loss of function, and disability [2]. RA may also result in bone complications such as peri-articular bone loss, bone erosions, and generalized osteoporosis [3–5]. RA is highly associated with significant bone mineral density (BMD) loss in femoral neck, lumbar spine, and generalized osteoporosis with an increased risk of fractures [6–9]. Multiple factors have been suggested to be involved in the higher prevalence of osteoporosis in patients with RA, with the osteoblast – osteoclast axis severely affected. This disruption occurs owing to the ongoing inflammatory process, which enhances osteoclast formation, immobility, and chronic treatment with corticosteroids [10,11]. The inherent risk factors for osteoporosis are aging and female sex [12]. Sclerostin (SOST) affects bone remodeling in both the normal and pathological stages [13,14]. SOST is a glycoprotein product of the SOST gene and is highly expressed in embedding bone cells such as osteocytes, chondrocytes, and cementocytes [15–17]. Several Wnt family members seem to be involved in the modulation of the inflammatory response during rheumatoid activity. Serum SOST levels are being investigated in various metabolic bone diseases. The

Wnt pathway has been shown to be important for the differentiation of osteoblasts from mesenchymal lineage precursors, and from endogenous Wnt inhibitors such as Dickkopf-1 (DKK-1), SOST, and secreted frizzled-related proteins. SOST might have important roles of osteoclast dysregulation in RA by inhibiting the Wnt/B-catenin canonical signaling pathway and binding to the low signaling lipoprotein receptor LRP-5/LRP-6, leading to decreased osteo-blastogenesis and osteoblast activity, and thereby decreasing bone formation [18,19]. SOST binds to bone morphogenic proteins as well as to LRP-5 and LRP-6, thus antagonizing bone morphogenic protein and Wnt signaling and enhancing osteoblast formation. As, SOST levels are decreased in primary hyperparathyroidism and elevated in hypoparathyroidism, parathyroid hormone is thought to be a regulatory factor for SOST. On the contrary, high serum SOST level in postmenopausal women is a risk factor for fractures. Several clinical studies have shown a significant increase of SOST levels with age and after menopause, suggesting that serum SOST may be associated with aging and menopause-induced bone loss [14,20,21]. Although glucocorticoid-induced osteoporosis and diabetes are both diseases that reduce bone formation, serum SOST levels have been reported to be decreased in the former and elevated in the latter. Serum SOST levels are correlated with renal function and increase with reduction in renal function, suggesting the difference in the effect of SOST in these diseases [22]. Serum SOST may be a new index of bone assessment that differs from BMD markers and other bone metabolic markers [23].

Table 1 Comparison between the two studied groups according to characteristics

Characteristics	Group [*n* (%)]		^{MC}P
	Cases	Controls	
Age (years)			
<40	9 (30.0)	12 (60.0)	0.041*
40–50	12 (40.0)	7 (35.0)	
≥50	9 (30.0)	1 (5.0)	
Range	18–70	23–50	
Mean±SD	44.1±11.2	36.0±8.1	
Sex			
Male	7 (23.3)	10 (50.0)	0.062
Female	23 (76.7)	10 (50.0)	

^{MC}P, Monte Carlo exact probability. *$P<0.05$, significant.

Table 2 Distribution of the studied patients regarding the disease severity indices

Disease severity indices	*N* (%)
DAS-28	
Mild	9 (30.0)
Moderate	16 (53.3)
Severe	5 (16.7)
HAQ score	
0	4 (13.3)
1	12 (40.0)
2	8 (26.7)
3	6 (20.0)

DAS, Disease Activity Score.

Aim

The aim of the work was to correlate the relation between level of serum SOST and BMD with disease severity in patients with RA.

Patients and methods

The study was conducted on 50 patients recruited from Alexandria Main University Hospital, Egypt. The 50 patients were divided into two groups: group I had 30 cases of RA diagnosed according to ACR/EULAR 2010 diagnostic criteria [24], and group II had 20 age-matched and sex-matched persons as a control group.

Inclusion criteria

Patients with RA were included.

Exclusion criteria

Patients with other connective tissue diseases as systemic lupus erythematosus, systemic sclerosis, and diabetes mellitus, patients on steroids, and patients with metabolic bone diseases were excluded.

Methods

All patients were subjected to the following: (a) thorough medical history taking, with specific stress on disease duration, duration of morning stiffness,

Table 3 Relation between Disease Activity Score-28 and demographic data of the patient group

Characteristics	DAS-28 [*n* (%)]			^{MC}P
	Mild	Moderate	Severe	
Age (years)				
<40	2 (22.2)	3 (33.3)	4 (44.4)	0.114
40–50	4 (33.3)	7 (58.3)	1 (8.3)	
≥50	3 (33.3)	6 (66.7)	0	
Sex				
Male	2 (28.6)	4 (57.1)	3 (12.0)	0.969
Female	7 (30.4)	12 (52.2)	2 (40.0)	
Family history				
Negative	8 (32.0)	14 (56.0)	3 (12.0)	0.307
Positive	1 (20.0)	2 (40.0)	2 (40.0)	
Disease duration (years)				
<5	3 (25.0)	6 (50.0)	3 (25.0)	0.749
5–10	4 (28.6)	8 (57.1)	2 (14.3)	
≥10	2 (50.0)	2 (50.0)	0	

DAS, Disease Activity Score; ^{MC}P: Monte Carlo exact probability.

Table 4 Relation between HAQ score and demographic data of the patient group

Characteristics of cases	HAQ score					^{H}P
	Mean	SD	Median	Minimum	Maximum	
Age (years)						
<40	1.9	1.2	2.0	0.0	3.0	4.1 (0.128)
40–50	1.7	0.7	2.0	1.0	3.0	
≥50	1.0	1.0	1.0	0.0	3.0	
Sex						
Male	1.7	1.0	1.0	1.0	3.0	*U*=0.22 (0.643)
Female	1.5	1.0	1.0	0.0	3.0	
Family history						
Negative	1.4	1.0	1.0	0.0	3.0	*U*=2.9 (0.050*)
Positive	2.2	0.8	2.0	1.0	3.0	
Disease duration (years)						
<5	1.5	0.9	1.5	1.0	3.0	1.8 (0.408)
5–10	1.5	0.9	1.5	0.0	3.0	
≥10	1.0	1.4	0.5	0.0	3.0	

H, Kruskal–Wallis test; *U*, Mann–Whitney test. *P<0.5, significant.

Table 5 Distribution of the studied patient group regarding the clinical and laboratory parameters

Clinical parameters	*N* (%)
CRP	
Negative	9 (30.0)
Positive	21 (70.0)
ANA	
Negative	24 (80.0)
Positive	6 (20.0)
Anti-CCP	
Negative	16 (53.3)
Positive	12 (40.0)
Equivocal	2 (6.7)
Rheumatoid factor	
Negative	18 (60.0)
Positive	12 (40.0)
Hb%	
Range	80.0–13
Mean±SD	10.6±1.0
Median	10.75
ESR 1	
Range	9–95
Mean±SD	42.6–25.6
Median	39
ESR 2	
Range	21–20
Mean±SD	68.2±29.3
Median	68

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin.

Table 6 Distribution of the studied patient group regarding dual-energy X-ray absorptiometry scan

DEXA	*n* (%)
Negative	6 (20.0)
Positive	24 (80.0)

DEXA, dual-energy X-ray absorptiometry.

Table 7 Relation between X-ray findings and dual-energy X-ray absorptiometry, Disease Activity Score-28, and HAQ

	Radiograph [*n* (%)]		Total [*n* (%)]
	Negative	Positive erosion	
DEXA scan			
Negative	6 (75.0)	0	6 (20.0)
Positive	2 (25.0)	22 (100.0)	24 (80.0)
Total	8 (100.0)	22 (100.0)	30 (100.0)
χ^2 (*P*)	20.62* (0.0001*)		
DAS-28			
Mild	1 (12.5)	8 (36.3)	9 (30.0)
Moderate	4 (50.0)	12 (54.5)	16 (53.3)
Severe	3 (37.5)	2 (9.1)	5 (16.7)
Total	8 (100.0)	22 (100.0)	30 (100.0)
χ^2 (*P*)	4.048 (0.256)		
HAQ score			
0	0	4 (18.2)	4 (13.3)
1	2 (25.0)	1 (45.5)	12 (40.0)
2	2 (25.0)	6 (27.3)	8 (26.7)
3	4 (50.0)	2 (9.1)	6 (20.0)
Total	8 (100.0)	22 (100.0)	30 (100.0)
χ^2 (*P*)	6098 (0.072)		

DAS, Disease Activity Score; DEXA, dual-energy X-ray absorptiometry. *P<0.5, significant.

number of swollen joints, and number of tender joints; (b) full clinical examination with specific stress on musculo-skeletal system examination; (c) determination of disease activity score by Disease Activity Score (DAS)-28 [25] and disability index (HAQ-DI) [26]; (d) laboratory tests, including complete blood count (CBC) [27], acute-phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] [28], rheumatoid factor [29], antinuclear antibody (ANA) titer using ELISA [30], anticitrullinated protein antibody using ELISA [31], and human SOST levels using ELISA technique [32]; (e) plain radiograph on both hands; and (f) ultrasound (US) for each hand and wrist for

detection of early bone erosions (including navicular, and lunate bones) and six joints [five metatarsophalangeal joints (MTPJs) and interphalangeal joints (IPJ)] for each foot.

The Svd H score defines erosions as follows: 0=no erosions (normal), 1=minor of discrete erosions, 2–3=larger erosions according to surface area involved, 4=erosions extending over the middle of the bone, 5=complete collapse, and 6=BMD assessment by dual-energy X-ray absorptiometry (DEXA) scan.

Table 8 Relation between the results of US and dual-energy X-ray absorptiometry, Disease Activity Score-28, HAQ score, and radiograph in the patient group

	US [*n* (%)]		*P*
	Negative	Positive	
DEXA scan			
Negative	1 (100.0)	5 (17.2)	χ^2=4.138 (^{FE}P=0.200)
Positive	0	24 (82.8)	
DAS-28 score			
Mild	0	9 (31.0)	χ^2=3.600 (^{MC}P=0.159)
Moderate	0	16 (55.2)	
Severe	1 (100.0)	4 (13.8)	
HAQ score			
0	0	4 (13.8)	χ^2=3.669 (^{MC}P=0.146)
1	0	12 (41.4)	
2	0	8 (27.6)	
3	1 (100.0)	5 (17.2)	
Radiographic findings			
Negative	1 (100.0)	7 (24.1)	χ^2=2.845 (^{FE}P=0.267)
Positive	0	22 (75.9)	

DAS, Disease Activity Score; DEXA, dual-energy X-ray absorptiometry; US, ultrasound; *U*: Mann–Whitney test. *$P<0.5$, significant.

Table 9 Comparison between the two studied groups regarding the sclerostin

Sclerostin (pg/ml)	Group		^{U}P
	Cases	Controls	
Range	2.4–165.9	6–103	3.4 (0.001)*
Mean	57.7	29.3	
SD	36.6	32.0	
Median	44.0	16.5	

U, Mann–Whitney test. *$P<0.05$, significant.

Results

Table 1 shows comparison between the two studied groups according to characteristics. There was a statistically significant difference between the two studied groups regarding age. Table 2 shows

Table 11 Correlation between sclerostin, Disease Activity Score-28, HAQ score, and US

Correlations	SOST (pg/ml)	
	r	*P*
DAS-28	0.25	0.191
HAQ score	–0.01	0.946
DEXA	0.221	0.240
Radiograph	0.165	0.382
US	–0.054	0.778

DAS, Disease Activity Score; DEXA, dual-energy X-ray absorptiometry; *r*: Spearman correlation co-efficient; SOST, sclerostin; US, ultrasound. Interpretation of *r*: Weak (0.1–0.24); Intermediate (0.25–0.74); Strong (0.75–0.99).

Table 12 Correlation between sclerostin, Hb%, ESR first hour, and ESR second hour

Correlation	Sclerostin (pg/ml)	
	r	*P*
Hb%	–0.12	0.524
ESR 1 h	–0.18	0.335
ESR 2 h	0.10	0.683

ESR, erythrocyte sedimentation rate; Hb, haemoglobin; *r*: Spearman correlation co-efficient. Interpretation of *r*: Weak (0.1–0.24); Intermediate (0.25–0.74); Strong (0.75–0.99).

Table 10 Relation between sclerostin and demographic data of patient group

Characteristics of cases	SOST (pg/ml)					^{H}P
	Mean	SD	Median	Minimum	Maximum	
Age (years)						
<40	55.1	37.2	42.7	6.0	127.6	0.75 (0.686)
40–75	54.0	40.5	44.0	2.4	165.9	
≥75	65.2	33.6	60.1	25.1	124.0	
Sex						
Male	40.3	31.1	36.9	6.0	103.8	*U*=2.3 (0.037)*
Female	63.0	37.1	50.8	2.4	165.9	
Family history						
Negative	57.4	37.7	44.2	2.4	165.9	*U*=0.01 (0.997)
Positive	59.6	38.4	43.7	35.6	127.6	
Disease duration (years)						
<5	46.5	25.7	41.4	6.0	103.8	8.8 (0.352)
5–10	71.8	44.5	56.8	2.4	165.9	
≥10	42.2	14.4	41.9	25.1	60.1	

H, Kruskal–Wallis test; SOST, sclerostin; *U*, Mann–Whitney test. *$P<0.05$, significant.

distribution of the studied patients regarding the disease severity indices (DAS-28 and HAQ-DI). Table 3 shows relation between DAS-28 and demographic data of the patients group. Table 4 shows relation between HAQ score and demographic data of patients group. Table 5 shows distribution of the studied patient group regarding the clinical and laboratory parameters of disease activity. Table 6 shows distribution of the studied patients group regarding DEXA scan. Table 7 shows relation between radiograph findings and DEXA scan, DAS-28 score, and HAQ score. Table 8 shows relation between the results of US and DEXA scan, DAS-28, HAQ score, and radiograph in RA group. Table 9 shows comparison between the two studied groups regarding the SOST. There was a statistically significant difference between the patient group and the control group regarding the SOST ($P<0.05$).

Table 13 Relation between the results of dual-energy X-ray absorptiometry scan and Disease Activity Score-28, sclerostin, and HAQ score in the patient group

	DEXA scan [*n* (%)]		^{MC}P
	Negative	Positive	
DAS-28			
Mild	0	9 (37.5	0.026*
Moderate	3 (50.0)	13 (54.0)	
Severe	3 (50.0)	2 (8.3)	
SOST (pg/ml)			
Range	6–103	2.4–165.9	U=1.2 (P=0.233)
Mean±SD	45.9±32.1	60.7±37.7	
Median	39.8	47.2	
HAQ score			
0	0	4 (16.7)	P=0.261
1	2 (33.3)	10 (41.7)	
2	1 (16.7)	7 (29.2)	
3	3 (50.0)	3 (12.5)	

DAS, Disease Activity Score; DEXA, dual-energy X-ray absorptiometry; SOST, sclerostin; *U*, Mann–Whitney test.

Table 10 shows the relation between SOST and demographic data of patients group. There was a statistically significant relation regarding sex ($P<0.05$). Table 11 shows the correlation between SOST and DAS-28, HAQ score, and US. Table 12 shows the correlation between SOST and haemoglobin (Hb%), ESR first hour, and second hour. Table 13 shows the relation between the results of DEXA scan and DAS-28, SOST, and HAQ score in the patient group. There was a statistically significant difference regarding DAS-28 ($P>0.05$). Table 14 shows the relation between SOST and clinical and laboratory parameters of disease activity in the patients group. Table 15 shows the relation between the results of US and DEXA scan, SOST, DAS-28 score, HAQ score, and radiograph in RA group.

Statistical analysis

Data shown are the mean±SEM. All statistical analyses for data were performed using SPSS software (SPSS software version 10). Data were analyzed between two groups using Student's *t*-test, whereas among more than two groups, data were analyzed by the one-way analysis of variance method. Differences of *P* value less than 0.05 were considered significant.

Discussion

SOST, the glycoprotein product of the SOST gene, is highly expressed in embedding bone cells such as osteocytes, chondrocytes, and cementocytes [15–17]. Several Wnt family members seems to be involved in the modulation of the inflammatory response during rheumatoid activity.

The Wnt pathway has been shown to be important for the differentiation of osteoblasts from mesenchymal

Table 14 Relation between sclerostin and clinical parameters in the patient group

Clinical parameters	Sclerostin (pg/ml)					^{U}P
	Mean	SD	Median	Minimum	Maximum	
CRP						
Negative	59.5	34.7	50.1	16.8	124.0	0.25 (0.803)
Positive	57.0	38.2	43.7	2.4	165.9	
ANA						
Negative	60.1	37.8	47.2	2.4	165.9	0.62 (0.534)
Positive	48.4	32.5	43.5	6.0	103.8	
Anti-CCP Abs						
Negative	63.2	39.4	47.5	16.8	165.9	1.2 (0.330)
Positive	48.6	35.5	41.9	2.4	124.0	
Equivocal	68.3	7.8	68.3	62.8	73.8	
Rheumatoid factor						
Negative	53.4	35.0	44.0	2.4	127.8	0.97 (0.330)
Positive	64.3	39.5	50.0	16.8	165.9	

ANA, antinuclear antibody; CRP, C-reactive protein; *U*, Mann–Whitney test.

Table 15 Relation between the results of US and dual-energy X-ray absorptiometry, sclerostin, Disease Activity Score-28, HAQ score, and radiograph in the patient group

	US [*n* (%)]		*P*
	Negative	Positive	
DEXA			
Negative	1 (100.0)	5 (17.2)	χ^2=4.138 (^{FE}P=0.200)
Positive	0	24 (82.8)	
SOST			
Range		2.40–165.90	*U*=0.289 (*P*=0.773)
Mean±SD	50.80±32.21	57.96±37.22	
Median		43.80	
DAS-28			
Mild	0	9 (31.0)	χ^2=3.600 (^{MC}P=0.159)
Moderate	0	16 (55.2)	
Severe	1 (100.0)	4 (13.8)	
HAQ score			
0	0	4 (13.8)	χ^2=3.669 (^{MC}P=0.146)
1	0	12 (41.4)	
2	0	8 (27.6)	
3	1 (100.0)	5 (17.2)	
Radiograph			
Negative	1 (100.0)	7 (24.1)	χ^2=2.845 (^{FE}P=0.267)
Positive	0	22 (75.9)	

DAS, Disease Activity Score; DEXA, dual-energy X-ray absorptiometry; SOST, sclerostin; US, ultrasound; *U*, Mann–Whitney test. *$P<0.5$, significant.

lineage precursors and endogenous Wnt inhibitors such as DKK-1 and SOST.

SOST might have important roles of osteoclast dysregulation in RA. This protein potently inhibits the Wnt/B-catenin canonical signaling pathway by binding to the low signaling lipoprotein receptor LRP-5/LRP-6, leading to decreased osteoblastogenesis and osteoblast activity, and thereby, decreasing bone formation [18,19].

Our results demonstrate that SOST serum levels were significantly increased in the RA group as compared with the control group. Regarding the relation between serum SOST and demographic data of the patients group, there was a statistically significant relation regarding sex ($P\leq0.05$). There was a positive correlation with the age of patients with RA and onset, which might indicate that the older the patients develop RA, the higher the SOST level they have, and this may later on predict a lower bone mass.

In agreement with this study, Francesco *et al.* [33] found no statistical significant correlation between DAS-28 and HAQ score.

Vis *et al.* [34] and Szulc *et al.* [35] found that SOST levels were significantly higher in female patients with RA than in healthy female controls.

In disagreement with this study, Mehaney *et al.* [22], confirmed by Polyzos *et al.* [36], did not find a significant difference in serum SOST between patients with RA and the control group.

Gennari *et al.* [37], confirmed by Amrein *et al.* [38] and Sheng *et al.* [39], found that serum SOST level was higher in males than in females. They explained that circulating SOST level might reflect total body skeletal mass. Accordingly, the larger skeleton in men might produce and release more SOST into the circulation [39].

There was a relation of serum SOST level with the disease activity in patients with RA using DAS-28. Vis *et al.* [34] have found that SOST level is negatively correlated to DAS-28 and correlated serum SOST level to radiological joint damage using van Der Heijde score. Vis *et al.* [34] found no correlation between van Der Heijde score and SOST levels. However, our results coincide with Vis *et al.* [34], found a negative correlation with disease activity using DAS-28 , not with whole DAS -28 score but with one of its variables which is the ESR. DKK-1, like SOST, is a national inhibitor of the Wnt signaling [40]. It was studied earlier than SOST in RA and plays a key role in the remodeling of bone and impairs local bone formation, which is particularly deleterious in RA [41].

Wang *et al.* [42] showed that DKK-1 levels in patients with RA was significantly higher than its levels in healthy controls. It was correlated with the Sharp score of radiological change (r=0.449, P=0.001) in patients with RA.

Gamze *et al.* [43] found that quantitative measurement of bone loss by DEXA scan may be a useful and practical outcome measure in RA and may be predictive for radiographic progression or functional status in patients with early RA. Human studies have shown a significant increase in serum SOST levels with age [14,20,38,44] and after menopause [20,44,45], suggesting that increased serum SOST may be associated with BMD loss induced by aging and menopause [14,20,44].

Other studies showed that increased serum SOST concentrations are associated with a greater risk of experiencing fracture in older postmenopausal women [25,38].

Several reports have demonstrated that RA is highly associated with significant BMD loss mainly in the femoral neck and lumbar spine, where there is greater risk for fracture in these anatomical sites [6–9,26,27].

This study did not determine fracture risk. We did find a significant BMD loss at both vertebral and femoral levels. This finding is in line with several studies demonstrating progressive loss of BMD during evolution of the disease in the right femur and at the vertebral level [9,12]. Given that patients with RA have a significantly lower BMD than healthy people and that SOST is a potent inhibitor of bone formation, it was initially predicted that serum SOST levels would negatively correlate with BMD in patients with RA.

However, this study results showed a positive correlation between femoral BMD and serum SOST in patients with RA. In partial agreement with our results, it was recently demonstrated that serum SOST levels have a positive correlation with vertebral BMD but not with femoral BMD [28].

Conclusion

This study has some limitations including small sample of patients with RA, most of patients were under treatment with disease-modifying antirheumatic drugs such as methotrexate, fracture risk was not determined in this study, and renal function was not measured.

However, it is possible that circulating SOST levels may not reflect changes of SOST at a local level.

Despite the many questions that remain, preclinical studies and clinical trial results would imply that SOST antibodies will emerge as a dominant first-line treatment in the management of osteoporosis.

Recommendations

Future longitudinal studies will identify whether SOST over-expression aggravates or slows down cardiovascular calcification. Lastly, it will be necessary to determine whether anti-SOST antibodies could slow the progression of vascular calcification or reduce the risk of cardiovascular events.

Future studies are needed to determine SOST levels at a local sites (bone, synovium, and bone marrow) and determine its association with disease progression and bone mineral density in patients with RA.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2008; 423:356–361.

2 Scott DL, Wolfe F, Huizinga TW, *et al.* Rheumatoid arthritis. Lancet 2010; 376:1094–1108.

3 Sambrook PN. The skeleton in rheumatoid arthritis: a common mechanisms for bone erosion and osteoporosis. J Rheumatol 2000; 27:2541–2542.

4 Lodder MC, Haugeberg G, Lems WF, *et al.* Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: The Oslo –Truro – Amsterdam (OSTRA) collaborative study. Arthritis Rheum 2003; 49:209–215.

5 Jensen T, Hansen M, Jensen KE, *et al.* Comparison of dual X-ray absorptiometry (DXA), digital X-ray radio-grammetry (DXR), and conventional radiograghs in the evaluation of osteoporosis and bone erosions in patients with rheumatoid arthritis. Scand J Rheumatol 2010; 34:27–33.

6 Gravallese EM. Bone destruction in arthritis. Ann Rheum Dis 2002; 61:84–86.

7 Forsblad-d'Elia H, Carlsten H. Bone mineral density by digital X-ray radiogrammetry is strongly decreased and associated with joint destruction in long standing rheumatoid arthritis: a cross-sectional study. BMC Musculoskelet Discord 2011; 12:242.

8 Schett G. Erosive arthritis. Arthritis Res Ther 2011; 9:S2.

9 Ardawi MS, Rouzi AA, Al-Sibiani SA, *et al.* High serum sclerostin predicts the occurrence of osteoporotic fractures in post-menopausal women: the Center of Excellence for Osteoporosis Research. J Bone Miner Res 2012; 27:2592–2602.

10 Hafez EA, Mansour HE, Hamza SH, *et al.* Bone mineral density changes in patients with recent onset rheumatoid arthritis. Clin Med Insights Arthritis Musculoskelet Discord 2011; 4:87–94.

11 Garnero P, Sornay-Rendu E, Munoz F, *et al.* Association of serum sclerostin with bone mineral density, bone turnover, steroids, and parathyroid hormone, and fracture risk in post-menopausal women: The OFELY study. Osteoporos Int 2013; 24:489–494.

12 Kim SY, Schneeweiss S, Liu J, *et al.* Risk of osteoporotic fracture in a large population – based cohort of patients with rheumatoid arthritis. Arthritis Res Ther 2010; 12:R154.

13 Roforth MM, Fujita K, McGregor UI, *et al.* Effects of age on bone mRNA levels of sclerostin and other genes relevant to bone metabolism in humans. Bone 2014; 59:1–6.

14 Modder UI, Hoey KA, Amin S, *et al.* Relation of age, gender, and bone mass to circulating sclerostin levels in women and men. J Bone Miner Res 2012; 26:373–379.

15 Van Bezooijen RL, Roelen BA, visser A, *et al.* Sclerostin is an osteocyte – expressed negative regulator of bone formation, but not a classical BMP antagonist. J Clin Endocrinol Metab 2014; 99:4740–4748.

16 Jager A, Gotz W, Lossdorfer S, *et al.* Localization of SOST/sclerostin in cementocytes in vivo and in mineralizing periodontal ligament cells in vitro. J Periodontal Res 2010; 45:246–254.

17 Van Bezooijen RL, Bronckers AL, Gortzak RA, *et al.* Sclerostin in mineralized matrices and Van Buchem disease. J Dent Res 2009; 88:569–574.

18 Li X, Zhang Y, Kang H, *et al.* Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. Biol Chem 2005; 280:83–87.

19 Poole KE, van Bezooijen RL, Loveridge N, *et al.* Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. FASEB J 2005; 19:1842–1844.

20 Ardawi MS, Al-Kadi HA, Rouzi AA, *et al.* Determinants of serum sclerostin in healthy pre-and post-menopausal women. J Bone Miner 2011; 26:2812–2822.

21 Arasu A, Pappoulos SE, Westdt ML, *et al.* Bone metabolism in rheumatoid arthritis: relation to disease activity. J Clin Endocrinol Metab 2012; 97:2027–2032.

22 Mehaney DA, Eissa M, Anwar S, *et al.* Serum sclerostin level among egyptian rheumatoid arthritis patients : relation to disease activity, bone mineral density and radiological grading. Acta Rheumatol Port 2015; 40:268–274.

23 Yamauchi M, Sugimoto T. Serum sclerostin levels and metabolic bone diseases. Clin Calcium 2013; 23:877–883.

24 Aletaha D, Neogi T, Silman AJ, *et al.* Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62:2569–2581.

25 Van Riel PL, Becker JC, Teng J, *et al.* Validation of the 28-joint Disease Activity Score (DAS-28) and European League Against Rheumatism Response criteria based on C-Reactive Protein against disease progression in patients with rheumatoid arthritis and comparison with the DAS-28 based on erythrocyte sedimentation rate. Clin Exp Rheumatol 2014; 32:64–74.

26 26Bruce B, Fries FJ. The standard health assessment questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003; 1:20.

27 Aletaha D, Neogi T, Silman AJ, *et al.* Rheumatoid arthritis classification criteria an : American college of Rheumatology/European league against rheumatism. Arthritis Rheum 2010;62:2569–2581.

28 Lant MJ, Willims AL, O' sullivan MM, *et al.* Relationship between time – integrated C-reactive protein level and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000; 43:1473–1477.

29 Sox HC, Liang MH. The erythrocyte sedimentation rate: guidelines for rational use. Ann Int Med 1986; 4:515–523.

30 Nell VP, Ebrel G, Storm TA. Benefit of very early therapy with disease modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology 2004; 43:906–914.

31 Kavanaugh A. Guidelines for clinical use of anti-nuclear antibody test and for specific auto-antibodies to nuclear antigens. Arch Pathol Lab Med 2009; 124:71–81.

32 Greiner A, Plischke H, Kellner H, *et al.* Association of anti-cyclic citrullinated peptide antibodies, rheumatoid factor, with serological parameters of disease activity in rheumatoid arthritis. Ann Rheum Dis 2009; 1050:295–303.

33 Fraccesco P, Goran R, Violeta V, *et al.* The role of Doppler ultrasound in rheumatic diseases. Rheumatology 2012; 16:10–15.

34 Vis M, Britsemmer K, Heijboer AC, *et al.* Sclerostin levels in rheumatoid arthritis and its relationship to disease activity and radiologic joint damage. Arthritis Rheum 2011; 63:1799.

35 Szulc P, Boutroy S, *et al.* Correlates of bone micro-architectural parameters and serum sclerostin levels in men. The STRAMBO study. J Bone Miner Res 2013; 28:169–178.

36 Polyzos S, Anastasilkis D, Bratengeier C, *et al.* Serum sclerostin levels positively correlate with lumbar spinal bone mineral density in post-menopausal women, the six month effect of risedronate and teriparatide. Osteoporos Int 2012; 23:1171–1176.

37 Gennari L, Merlotti D, Valenti R, *et al.* Circulating sclerostin levels and bone turnover in type 1 and type 2 diabetes. J Clin Endocrinol Metab 2012; 97:1737–1744.

38 Amrein K, Amrein S, Drexler C, *et al.* Sclerostin and its association with physical activity, age, gender, body composition, and bone mineral content in healthy adults. J Clin Endocrinol Metab 2012; 97:148–154.

39 Sheng Z, Tong D, Ou Y, *et al.* Serum sclerostin levels were positively correlated with fat mass and bone mineral density in Central South Chinese postmenopausal women. Clin Endocrinol (Oxf) 2012; 76:797–801.

40 Glinka A, Wu W, Delius H, *et al.* Dickkopf-1 is a member of a new family of secreted proteins. Nature 1998; 391:357–362.

41 Diarra D, Stolina M, Polzer K, *et al.* Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007; 13:156–163.

42 Wang SY, Liu YY, Ye H, *et al.* Circulating Dickkopf-1 is correlated with bone erosion and inflammation in rheumatoid arthritis. J Rheumatol 2011; 38:821–827.

43 Gamze JR, Salih AJ, Young T, *et al.* The precision of digital X-ray radiogrammetry compared with DEXA scan in subjects with normal bone density or osteoporosis. J Clin Densitom 2014; 8:187–190.

44 44Mirza FS, Padhi ID, Raisz LG, *et al.* Serum sclerostin levels negatively correlated with parathyroid hormone levels and free estrogen index in postmenopausal women. J Clin Endocrinol Metab 2010; 95:1991–1997.

45 Costa AG, Walker MD, Zhang CA, *et al.* Circulating sclerostin levels and markers of bone turnover in Chinese – American and white women. J Clin Endocrinol Metab 2013; 98:4736–4743.