ASDJ
AINSHAMS DENTAL JOURNAL

Print ISSN 1110-7642
Online ISSN 2735-5039

AIN SHAMS DENTAL JOURNAL
Official Publication of Ain Shams Dental School
June2025 • Vol. 38

Is sclerostin a reliable biomarker for disease severity? Evaluation of sclerostin levels in the serum and gingival crevicular fluid of rheumatoid arthritis patients with periodontitis: A case–controlled study

Aya Ali Ahmed Hussien[1], Omnia B. Attia[2]
Ebtehal Mohammed[3], Mahetab Abdal-Wahab[4]

Aim: In the present study, we selected Rheumatoid arthritis (RA) with stage III periodontitis as both diseases are characterized by bone loss to evaluate the reliability of sclerostin, as a biomarker for disease severity, in both the serum and gingival crevicular fluid (GCF).
Materials and methods: A total of 36 participants were included in this study, with 12 participants in each group: patients with RA with stage III periodontitis, healthy patients with stage III periodontitis and healthy controls. Serum samples and GCF samples were collected from the pocket with greatest clinical attachment loss in periodontitis patients and the gingival sulcus of healthy controls. The sclerostin concentration in the samples was assessed by enzyme-linked immune assay (ELIZA).
Results: There was no significant difference between the serum or GCF sclerostin levels of the three groups. Additionally, there was no association between the serum and GCF sclerostin levels among or within the groups.
Conclusion: Among the limitations of the present study, sclerostin did not reflect the severity of periodontitis or RA. However, it may reflect the disease activity with further studies are recommended.

Keywords: Sclerostin, disease biomarker, periodontitis, rheumatoid arthritis.

1. Oral Medicine and Periodontology, Faculty of Dentistry, Egyptian Russian University, Cairo, Egypt.
2. Internal Medicine Department, Rheumatology Division, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
3. Oral Medicine and Periodontology Department, Faculty of Dentistry, Beni-Suef University, Beni-Suef, Egypt.
4. Department of Oral Medicine, Periodontology, Oral Diagnosis and Radiology, Faculty of Dentistry, Ain Shams University, Cairo, Egypt.
Corresponding author: Ebtehal Mohammed, email: ebtehalmaawad@dent.bsu.edu.eg

Introduction

Sclerostin is emerging as an important regulator of bone homeostasis. Its role in many bone-associated diseases, such as osteoporosis, osteoarthritis, osteonecrosis, bone tumors and osteogenesis imperfecta, as well as many chronic diseases, such as rheumatoid arthritis, ankylosing spondylitis, diabetes mellitus and periodontitis, has been investigated. [1, 2]

Sclerostin is a secreted glycoprotein that is expressed mainly by mature osteocytes and has a direct negative effect on bone formation and an indirect positive effect on bone resorption. [3] It has an inhibitory effect on the canonical Wnt signaling pathway, which plays an essential role in bone formation and bone remodeling. By binding Wnt proteins to the surface receptors LRP5/6, Wnt/β-catenin signaling is activated with subsequent differentiation of stem cells into osteoblasts. Sclerostin promotes osteoblast maturation, and the survival of both osteoblasts and osteocytes Sclerostin has the ability to enhance the expression of osteoprotegerin (OPG), thus inhibiting osteoclast differentiation. Sclerostin, a Wnt pathway regulator, binds to LRP5/6, blocking Wnt/β-catenin signaling and thus inhibiting osteoblast differentiation from progenitors. Sclerostin has multiple effects on osteoblasts; it inhibits the maturation of late osteoblasts to osteocytes, downregulates osteoblast activity by decreasing alkaline phosphatase expression, and enhances osteoblast apoptosis. [4]

RANK/RANK osteoclastogenesis is dependent on the binding of receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) to receptor activator of NF-κB (RANK) on osteoclast progenitors for differentiation into osteoclasts. OPG is a decoy receptor of RANKL, so the OPG:RANKL ratio is an important determinant of bone metabolism. By inhibiting Wnt/β-catenin signaling, sclerostin is suggested to have an indirect positive effect on osteoclastogenesis and enhancing bone resorption through the downregulation of OPG expression and the upregulation of RANKL expression by osteocytes . Additionally, it was suggested to have an additional indirect effect by decreasing colony stimulating factor-1 and increasing WNT1-induced secreted protein 1, two important osteoclastogenesis regulators. [5]

Rheumatoid arthritis (RA) is an autoimmune disease characterized by regional bone loss affecting mainly the synovial joints, leading to damage, as well as systemic bone loss that may lead to osteoporotic fracture. Both regional and systemic bone loss are attributed to enhanced osteoclast-mediated bone resorption and inhibited osteoblast-mediated bone formation, suggesting the involvement of sclerostin in RA pathogenesis. Based on this assumption, sclerostin expression should be increased in RA patients; however, both animal studies and clinical studies have shown contradictory results. [6]

Periodontitis is defined as a chronic inflammatory disease of the supporting tooth apparatus, including the gingiva, periodontal ligament, cementum, and alveolar bone. It is caused primarily by dysbiotic dental biofilms triggering the host immune response, which is modified by host-related systemic and local factors and is responsible for disease progression.[7] According to the WHO oral health report 2022, periodontitis affects approximately 20% of the adult population, and periodontitis is linked to many other systemic diseases, including rheumatic arthritis, which is attributed to the infiltration of immune cells, the release of inflammatory cytokines, increased

expression of RANKL, and shared risk factors.[8] The association of sclerostin with periodontitis has been suggested, as sclerostin is upregulated by many proinflammatory cytokines that are involved in periodontitis, including TNF-α, IL-β and activated NF-κβ. [1]

Many studies have shown increased levels of sclerostin in periodontitis patients compared with healthy individuals and have indicated sclerostin as a disease biomarker. [9]

In a previous study, we investigated the sclerostin level in three different periodontitis groups, periodontitis nondiabetic, periodontitis with controlled diabetes and periodontitis with uncontrolled diabetes, and there was no significant difference among the three groups in terms of the sclerostin level in gingival crevicular fluid. The authors concluded that periodontitis has a greater effect on the local sclerostin level in periodontal pockets than does diabetes, but the study did not evaluate the sclerostin level in a healthy population compared with that in periodontitis patients. [10]

To our knowledge, no previous study has investigated the level of sclerostin in periodontitis patients with rheumatoid arthritis, so the present study investigated the level of sclerostin in periodontitis patients with rheumatoid arthritis in both the serum and GCF and periodontitis patients without RA. Then, they were compared with the healthy group to evaluate whether sclerostin is a reliable biomarker for the severity of these two chronic inflammatory diseases, which are characterized by bone loss.

The null hypothesis was that there would be no difference in sclerostin levels in either the serum or GCF between healthy controls, periodontitis patients and periodontitis with rheumatoid arthritis patients. However, an alternative hypothesis is that sclerostin is upregulated by proinflammatory cytokines, and because of its role in bone loss, there was a significant difference in the serum and GCF sclerostin levels in periodontitis patients with RA, followed by periodontitis only, compared to those in healthy patients.

Materials and methods

Study design

The present case–control study included 36 patients, both males and females, who were divided into three groups:

Group I included rheumatoid arthritis patients with stage III periodontitis.

Group II included healthy patients with stage III periodontitis according to the American Society of Anesthesiologists (ASA). [11]

Group III included healthy patients who had a healthy periodontium according to the American Society (ASA) classification system.

All the procedures performed in this study were carefully explained to the patients, and all the patients who participated in this study signed an informed consent form before being enrolled in the study. The study was conducted from October 2023 to February 2024. Patients in group I were recruited from the outpatient clinic of the Rheumatoid Department, Faculty of Medicine, Ain Shams University. Patients in groups II and III were recruited from the Periodontology Clinic, Faculty of Dentistry, Egyptian Russian University. All the procedures performed in this study were reviewed and approved by the Ethical Committee of the Faculty of Dentistry, Egyptian Russian University (FD-ERU-REC), with a final registration number (FD-ERU-REC-12).

Sample size calculation

The sample size was calculated using G*Power version 3.1.9 software.[12] The total sample size was 20 participants. This sample size calculation was based on an anticipated effect size of 1.7 obtained from, [13] aimed at detecting significant differences in sclerostin levels between patients with rheumatoid arthritis (Group 1) and healthy controls (Group 3). The statistical power was set to 95%, ensuring a high likelihood of detecting a real difference if it exists, with an alpha level set at 0.05 for a two-sided test. To increase the accuracy of the results, the authors increased the total sample size to 36, i.e., 12 samples from each group were used to detect differences in sclerostin levels in the GCF and serum of the patients.

Study population

The present study included 36 patients aged 30-60 years. For the rheumatic patients (group I), all the patients fulfilled the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA.[14] All of them had had RA for more than one year; had no cardiac events, diabetes, or any complications secondary to RA; and did not receive previous intra-articular drug injections.

Patients in groups II and III had no systemic disease according to the American Society of Anesthesiologists (ASA) classification system. Other exclusion criteria included the following: (1) pregnant female and smoking patients for whom periodontitis is a well-known risk factor, [15] (2) patients who underwent either surgical or nonsurgical periodontal therapy for the last 6 months, and (3) patients who had received antibiotics for the last 3 months.

One rheumatologist was responsible for rheumatic examination and selection of the patients in group I. Selected rheumatic patients in group I were subjected to GCF sampling and serum sampling by an experienced periodontist who was blinded to all groups.

Periodontal Examination

Periodontal examination and visualization using a UNC-15 probe were performed by an experienced periodontist who was blinded to all the groups. Periodontal diagnosis was performed according to the guidelines of the new 2017 classification. Patients were diagnosed with gingival health or a healthy periodontium if they had no clinical attachment loss (CAL), a probing depth < 3 mm or bleeding points in less than 10% of the sites. Patients were diagnosed with stage III periodontitis if they had a CAL ≥ 5 mm, radiographic bone loss extending to the apical third of the tooth and tooth loss due to periodontal disease < 4 teeth.[16]

GCF sample collection

The GCF samples were taken from the most representative tooth (the site with the greatest CAL). Careful water and air spray were used to remove any loose debris, and then the site of interest was dried with sterile gauze to prevent sample contamination with saliva. The GCF was collected with endodontic absorbent paper points (Meta Biomed Co. Ltd., Cheongju, Korea), which were inserted deeply into the sulcus tooth for 30 seconds. Two strips were withdrawn from each patient to make one sample. The paper strips were immediately sealed in Eppendorf tubes® (Eppendorf AG, Hamburg, Germany) with a phosphate-buffered saline solution (Invitrogen, Camarillo, CA, USA). Strips visually contaminated with blood or saliva were excluded. The collected samples were diluted to a dilution factor of 250 µl and immediately stored at −80°C until the

day of laboratory analysis. Sclerostin levels were analyzed using an enzyme-linked immunosorbent assay with a Human Sclerostin ELISA Kit (BT Lab, Shanghai, China; Cat. no. E3068Hu).

Serum sample collection

Venous blood was drawn from each patient, and the blood was centrifuged to isolate the serum. The serum samples were immediately stored at −80°C until the day of laboratory analysis. Sclerostin levels were analyzed using an enzyme-linked immunosorbent assay with a Human Sclerostin ELISA Kit (BT Lab, Shanghai, China; Cat. no. E3068Hu).

Statistical analysis plan

The data were statistically analyzed using SPSS version 28.0 for Windows. The levels of sclerostin in the GCF and serum for the three groups were summarized using the mean, standard deviation, median, and range for both the serum and GCF. The Kruskal–Wallis H test, a nonparametric method, was utilized to compare the medians of sclerostin levels among the groups, as appropriate because of the nonnormal distribution of the data, as evidenced by the Kolmogorov–Smirnov and Shapiro–Wilk tests, as well as the wide ranges and variability in standard deviations. Statistical significance was determined with a *p value* threshold of less than 0.05. Furthermore, we explored the relationship between serum and GCF sclerostin levels within the overall cohort and within each group separately using Spearman's correlation coefficient, given the skewed distributions of sclerostin levels.

Results

The differences in the serum and GCF sclerostin levels among the three groups were not statistically significant, with *p - values* of 0.182 and 0.365, respectively. However, patients with periodontitis in the RA group had slightly greater serum sclerostin levels than patients with periodontitis only or healthy controls. The healthy controls had slightly greater GCF sclerostin levels than periodontitis patients and periodontitis patients (Table 1).

Table 1: Distribution of serum and GCF sclerostin levels among the study groups

		Group 1 (RA+Periodontitis)	Group 2 (Periodontitis only)	Group 3 (Healthy control)	P value
Serum Sclerostin level (ng/ml)	Mean ± SD Median Range	8.9 ± 20.3 2.8 2.4 - 73.3	8.3 ± 11.5 3.2 2.9 - 33.5	7.05 ± 9.2 3.04 1.2 – 27.04	0.182
GCF sclerostin level (ng/ml)	Mean ± SD Median Range	7.1 ± 1.1 6.6 6.2 - 9.8	7.4 ± 1.7 7 5.1 - 10.7	7.6 ± 0.93 7.8 5.9 - 8.8	0.365

SD= standard deviation.

The Kruskal–Wallis H test was used to compare the medians across each group; a P value less than 0.05 indicated a significant difference.

Additionally, no correlation was found between serum and GCF sclerostin in any of the groups or within each group separately, as shown in Table 2.

Table 2: Correlations between serum and GCF sclerostin levels in all groups

	Sperman correlation coefficient with 95% CI	*P value*
Overall cohort	-0.111 (-0.432, 0.235)	0.519
Group one (RA with periodontitis)	-0.007 (-0.591, 0.582)	0.983
Group two (Periodontitis without RA)	-0.126 (0.697, 0.498)	0.697
Group three (Healthy control)	-0.357 (-0.780, 0.291)	0.255

CI= Confidence interval; the Spearman correlation coefficient was used to correlate serum and saliva sclerostin levels in all groups.

Discussion

The current study aimed to evaluate sclerostin in the serum and gingival crevicular fluid as a biomarker of disease severity for

periodontitis and rheumatoid arthritis, which are chronic inflammatory disorders.

Sclerostin, a negative regulator of bone formation and a positive regulator of bone resorption, is suspected to be a sensitive biomarker for diseases characterized by bone loss, [17] such as periodontitis and rheumatoid arthritis.

Clinical and radiographic assessments refer to retrospective tissue destruction and cannot predict disease progression. However, biomarkers are reliable diagnostic tools for current disease severity as well as for predicting disease progression.[18] GCF sampling represents a noninvasive, site specific, independent and reliable diagnostic tool with a very important role in understanding the role of different molecules in disease processes. [19]

Periodontitis is a polymicrobial disease characterized by a host-mediated inflammatory response leading to periodontal tissue destruction that may progress to tooth loss.[20] The pathological apical migration of the junctional epithelium clinically measured by clinical attachment loss (CAL) is the hallmark of the transition from irreversible gingivitis to periodontitis, which is irreversible tissue destruction. [21] According to the new 2017 classification of periodontal diseases and conditions, periodontitis is defined as detectable clinical attachment loss (CAL) in more than 2 nonadjacent sites with further staging of disease based on disease severity, which is mainly represented by the degree of CAL.[16] In the present study, we selected patients with stage III periodontitis because it is associated with significant bone loss and is reliable for the assessment of sclerostin levels as a disease biomarker.

RA is an autoimmune disorder characterized by chronic inflammation leading to progressive joint destruction and deformity, and as a systemic disorder, it usually affects other systems, including the cardiovascular system, lung, kidney, metabolism, and osteoporosis.[22]

In the present study, we selected RA patients without associated cardiovascular disease, diabetes, or other possible systemic complications and who received intra-articular injections that may have affected the sclerostin level.[22,23]

In the present study, we selected RA because it shares many pathological features with periodontitis. Both periodontitis and RA are chronic inflammatory conditions that are characterized by immune cell infiltration, increased proinflammatory cytokine levels, and most importantly, activation of the RANK-RANKL pathway involved in bone resorption;[24] thus, these conditions are more suitable for investigating sclerostin levels as a disease biomarker.

The present study investigated the sclerostin level in the GCF related to the site with the greatest CAL in patients with stage III periodontitis, in patients with RA (group I), in patients without RA (group II) and in healthy patients without periodontitis or RA (group III) and correlated the level of sclerostin in the GCF, reflecting its level in the local environment, to the serum sclerostin level, reflecting its systemic level, to evaluate sclerostin as a reliable biomarker for the disease activity of periodontitis and RA.

The present study revealed no statistically significant differences in the serum or GCF sclerostin levels among the 3 groups (*p* values of 0.182 and 0.365, respectively), with a slightly greater increase in the serum sclerostin level in the RA with periodontitis group.

To our knowledge, no previous study has investigated sclerostin levels in periodontitis patients with periodontitis. However, in comparison to other studies investigating sclerostin levels in RA patients, the results of the current study were consistent with those of another study conducted among 40 Egyptian patients and showed no significant difference

in serum sclerostin levels compared with those in healthy controls.[25] Additionally, many other studies have shown no significant difference in the serum level of sclerostin between patients with RA and healthy controls. [6,26,27,28] In contrast, many other studies have shown higher serum sclerostin levels in individuals with RA than in healthy controls, [13, 29,30] and another study showed higher levels of serum sclerostin but not disease activity or bone mineral density[31]. Similarly, another study conducted among the Egyptian population showed that the serum sclerostin level was greater in patients with RA than in healthy controls; however, the sclerostin level was not correlated with disease activity, and the authors concluded that sclerostin could not be considered a prognostic disease biomarker. [32]

We investigated RA in patients who were receiving antirheumatic treatment, mainly methotrexate and nonsteroidal anti-inflammatory agents, from outpatient clinics, and most of them were controlled. [33] Only a high value (73 ng/ml) was recorded for a female patient who recovered recently from hospital admission, which might explain our results. Additionally, RA is characterized by the death of osteocytes, which are responsible for sclerostin synthesis, decreasing the level of sclerostin released into the circulation.[34]

In the group with periodontitis without RA, the sclerostin level in the serum and GCF did not differ from that in the group with RA or healthy controls. These results were similar to our previous study,[10] which showed no difference in sclerostin levels between patients with periodontitis only and patients with controlled or uncontrolled diabetes in the GCF. Another study showed no difference in sclerostin levels between patients with periodontitis and healthy controls; however, sclerostin levels were greater in patients with gingivitis,[35] and the authors concluded that sclerostin levels may reflect the stage of periodontal disease and its activity and chronicity, as in early disease, there was initiation of active bone destruction, while in advanced disease, as in stage III periodontitis, the bone was already destroyed with a decreased level of sclerostin, and in healthy controls, there was no stimulus to increase sclerostin release. Additionally, these results were confirmed by,[36] who showed no difference in the GCF sclerostin level between patients with stage III periodontitis of grade B or C, confirming that the loss of bone is associated with a decreased level of sclerostin regardless of disease prognosis. In a recent study, [37] there was no correlation between sclerostin GCF level and disease severity or anti-inflammatory treatment by statins or dickkopf-1 (DKK-1), another inhibitor of the Wnt-β pathway.

In contrast to the results of the present study, several studies have shown a significant increase in sclerostin levels in periodontitis patients Shruthi , et al.[9] However, not all these studies applied similar methodologies. The heterogenicity of methodology included the investigation of mRNA in gingival tissues by PCR, selection of periodontitis according to older classification (American Academy of Periodontology 1999), which included different disease stages and severities of periodontitis. Additionally, the discrepancy in the use of different sclerostin methods has led to contradictory results regarding the same conditions or disease as in a study that was conducted to evaluate the serum sclerostin levels of 186 healthy adults using three different assay methods. [38] The results differed for the same individuals with very low sclerostin levels recorded by one assay method, and the author suggested that this low level was determined by measuring intact sclerostin rather than circulating sclerostin as with the other two methods.

In the present study, there was no significant correlation between the serum and GCF sclerostin levels among the study groups or among the groups; this could be expected

because the GCF reflects the local environment of the periodontal tissues, and the regulation of serum sclerostin is affected by various factors, including age, estrogen level, vit D, parathyroid hormones, mechanical stresses, physical activity, glucocorticoids, and systemic proinflammatory cytokines.[1]

A narrative review by Omran et al., [39] revealed that it is not possible to compare sclerostin levels among different studies for many reasons, including the wide discrepancy of assay methods. First, most available kits assess circulating fragmented sclerostin, while there are only a few kits available for assessing intact/bioactive sclerostin. Second, most of these kits are ELIZA kits, which are widely different in terms of sensitivity, assay range and turnover time. Third, most of these kits are not provided by the standards used for the manufacturing assay, except for a few manufacturers.

Despite the shortcomings of the small sample size of the current study, the need for more different groups to compare, for example, different stages of periodontitis and RA during disease exacerbation and remission and before and after treatment, we concluded that sclerostin may not be a reliable disease biomarker for periodontitis and RA in the clinical setting, However, it may be related to disease activity, based on the odd value of recently recovered RA patient from hospital admission.

Conclusion

Among the limitations of the present study, sclerostin did not reflect the severity of periodontitis or RA, further studies are recommended to investigate its value as biomarker for disease activity.

Funding: The study was self-funded.

Data availability: The data are available on request from the authors.

Ethics approvals and: All the procedures performed in this study were reviewed and approved by the Ethical Committee of the Faculty of Dentistry, Egyptian Russian University (FD-ERU-REC), with a final registration number (FD-ERU-REC-12).

Consent to participants: All participants signed an informed consent before being enrolled in this study.

Competing interests: All authors declare that they have no conflict of interest.

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