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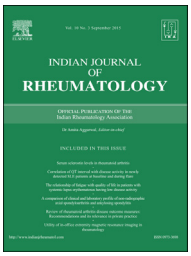

Original Article

Serum sclerostin levels in rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease that may lead to joint destruction and disability. Wingless (Wnt) pathway is involved in bone formation and has been found to contribute to bone loss in RA. Sclerostin is a key molecule in Wnt pathway.
Objective: To study the serum levels of sclerostin in rheumatoid arthritis patients and to study its association with radiological changes.
Methods: Forty-five patients with RA and 45 age and gender matched healthy controls were enrolled. Serum sclerostin was measured by ELISA. Modified version of Larsen score was used to assess joint damage in radiographs and Magnetic resonance imaging (MRI) of wrist and hand was assessed for synovitis and bone erosion.
Results: Serum sclerostin levels were higher in patients with RA as compared to controls ($p < 0.01$). Serum sclerostin levels correlated with ESR ($r = 0.655$), CRP($r = 0.623$), modified DAS 28 ($r = 0.711$), MRI synovitis ($r = 0.802$) and MRI erosion score ($r = 0.832$).
Conclusion: Increased serum levels of sclerostin may play a role in joint damage and bone erosion in RA.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that may lead to joint destruction and disability.[1] In addition to inflammation of the synovium, a major clinical manifestation of RA is the progressive destruction of bone and cartilage leading to bone erosion and joint space narrowing.[2] A hallmark of RA pathogenesis is an imbalance of the osteoblast–osteoclast axis driven by inflammatory processes, resulting in elevated bone resorption.[3] The formation and activation of osteoclast at the cartilage pannus junction is an essential step in the destruction of bone matrix in patients with RA.[4] Since joint destruction caused by RA is irreversible, early diagnosis and initiation of treatment are essential in maintaining patients' quality of life.

Several key molecules are involved in the regulation of osteoclast differentiation, such as receptor activator of nuclear factor kappa B ligand (RANKL), which are induced by inflammation. It plays an important role in osteoclast-mediated

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destruction of the joint architecture. Osteoprotegrin is a decoy receptor of RANKL, which competes with RANKL receptor for ligand binding and thus prevent RANKL biologic activities.[5]

The Wnt family of glycoproteins is involved in the regulation of multiple cellular activities, including bone formation and remodeling.[6] The Wnt/β-catenin pathway involves the binding of Wnt proteins to a coreceptor complex, comprising low-density lipoprotein receptor-related protein LRP5 or LRP6 and a member of the frizzled (Fz) family of proteins. This interaction eventually leads to an increase of the intracellular β-catenin levels through inhibition of the β-catenin degradation complex. Wnt/β-catenin pathway play an important role in bone mass regulation and osteoclastogenesis in RA and osteoarthritis (OA).[7]

Sclerostin is a Wnt inhibitor, specifically expressed by osteocytes, which inhibits osteoblast-driven bone formation and induces mature osteoblast apoptosis.[8] Sclerostin deficiency leads to sclerosteosis.[9] Elevated sclerostin is implicated in the mechanisms of bone loss in metabolic bone diseases, such as postmenopausal osteoporosis and thalassemia associated osteoporosis.[10] Sclerostin, an osteocyte-specific protein and product of the sclerostin gene (*SOST*), is a potent suppressor of bone formation. Low or absent sclerostin expression can occur as a consequence of osteocyte death or genetic mutation, which leads to enhanced bone apposition.[11]

Osteoclasts have been shown to be the principle cells that mediate bone erosion in RA, and studies have revealed that functional osteoclasts are found within few days of inflammation onset.[12]

The aim of this study is to measure the serum levels of sclerostin in patients with RA and to see its association with radiological changes.

2. Patients and methods

This study was conducted on 45 rheumatoid arthritis patients diagnosed according to the recent 2010 ACR-EULAR classification.[13] All patients were recruited from the outpatient clinic of Rheumatology & Rehabilitation and Internal medicine departments of Ain Shams university hospitals. Forty five healthy volunteers served as a control group. Informed consents were taken from each patient and control. The study was approved by Ain Shams medical ethical committee.

RA patients previously treated with biologics, or having metabolic bone disease including osteoporosis, malignancy, medication that could affect bone metabolism, previous radiation therapy, and abnormal thyroid, liver and kidney function patients were excluded from the study. None of the patients had received oral or intra-articular corticosteroids 6 weeks prior to the study.

All patients underwent a detailed clinical examination, complete blood count, erythrocyte sedimentation rate (ESR), C- reactive protein (CRP) and Rheumatoid factor (RF) by latex method were done. ELISA was used to measure anti-cyclic citrullinated peptide antibodies (anti-CCP) and serum sclerostin (Tico medical, Quidal corporation, USA)

- Disease activity of RA patients was assessed using the modified disease activity score (DAS 28).[14]
- Plain X-ray of hands, wrists and feet were assessed by the modified version of Larsen score.[15]
- MRI imaging of the dominant or clinically more affected wrist was done to RA patients. MRI scoring of RA wrist and hand was performed according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group RA-MRI scoring (RAMRIS) system.[16] Synovitis was scored on a 0–3 scale at 3 different locations: distal radio-ulnar joint, radiocarpal joint and intercarpal-carpometacarpal joint (total maximum score 9). The 0° indicate a normal state, while the degrees from 1 to 3 (mild, moderate, severe) refer to increments of one third of the presumed maximum volume of enhancing tissue in the synovial compartment. Bone erosions were scored on a 0–10 scale based on the proportion of eroded bone compared with assessed bone volume at carpal bones, distal radius, distal ulna and metacarpal bones (15 locations), where 0: no erosion, 1: 1–10% of bone eroded, 2: 11–20%, 3: 21–30%, 4: 31–40%, 5: 41–50%, 6: 51–60%, 7: 61–70%, 8: 71–80%, 9: 81–90%, 10: 91–100%. The maximum score for bone erosion is 150.

Two groups were compared using student t test and correlation was done using Spearman's Rank correlation.

3. Results

Patients with RA (35 females and 10 males) had mean age of 49.47 ± 7.17 years and mean disease duration of 7.8 ± 4.69 years.

Healthy controls (33 females and 12 males) had mean age of 51.09 ± 6.74 years and had mean ESR of 7.43 ± 1.81 mm/hour and mean CRP of 4.04 ± 1.18 mg/dl.

Patients with RA had mean ESR was of 37.33 ± 25.9 mm/hour, mean CRP of 24.89 ± 14.77 mg/dl and mean DAS of 5.23 ± 2.6. The mean modified Larsen score in patients was 74.93 ± 41, MRI synovitis score was 5.16 ± 2.56 and MRI erosion score was 75.78 ± 36.63.

The mean serum levels of sclerostin were higher in patients with RA (11.15 ± 12.05 ng/ml) as compared to control group (2.33 ± 0.97 ng/ml) ($p < 0.01$).

There was a significant positive correlation between serum sclerostin levels in RA patients and ESR ($r = 0.655$), CRP ($r = 0.623$), modified DAS 28 ($r = 0.711$), MRI erosion score (Fig. 1) and MRI synovitis (Fig. 2).

4. Discussion

Rheumatoid arthritis leads to generalised as well as periarticular bone loss and cartilage damage.[17] Bone and cartilage loss contribute to joint damage and increased fracture risk.[18] Inflammation creates an imbalance in bone homeostasis with high rate of resorption with low bone formation. Even biological cause only partial improvement in bone loss.[19]

Sclerostin, an osteocyte-specific protein and product of the sclerostin gene (SOST) is a potent suppressor of bone formation. In RA, variants of the SOST gene have been linked to structural progression of disease.[20]