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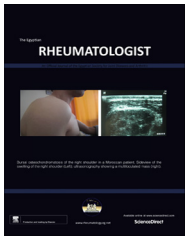

ORIGINAL ARTICLE

# Osteoprotegerin (OPG) and Matrix Gla protein (MGP) in rheumatoid arthritis patients: Relation to disease activity

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**KEYWORDS**

Rheumatoid arthritis (RA);
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Disease activity score 28-CRP (DAS28-CRP)

**Abstract** *Background:* Imbalanced Matrix Gla protein (MGP) and Osteoprotegerin (OPG) levels occur in inflammatory diseases.

*Aim of the work:* The aim of the present study was to evaluate serum MGP and OPG levels in Rheumatoid Arthritis (RA) patients and study their relation to the disease activity.

*Patients and methods:* Forty-five female RA patients and 45 age and sex-matched healthy controls were included in this study. Disease activity score 28-C-reactive protein (DAS28-CRP) was used for the assessment of disease activity. High-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), MGP and OPG were measured in patients and controls. The associations of MGP and OPG with DAS28-CRP and the other laboratory and clinical variables were analyzed.

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*Results:* RA patients had significantly higher serum OPG levels (408.3 ± 520.9 pg/ml) and hs-CRP (2.8 ± 1.9 mg/l) than the control (92.5 ± 86.3 pg/ml and 0.9 ± 1.5 mg/l respectively) ($p < 0.001$ each). There was no significant difference in MGP levels between the patients and control ($p = 0.3$). The correlation of OPG and MGP with DAS28-CRP in the patients was insignificant ($p = 0.4$ and $p = 0.8$ respectively). Age positively correlated with OPG ($r = 0.32$, $p = 0.02$), but not with MGP concentration ($r = 0.05$, $p = 0.64$) in the RA patients.

*Conclusions:* The significant elevation of the OPG level in RA patients may through light on its possible role in the pathogenesis of this disease and could be considered as a future therapeutic target. The significant correlation with age suggests that OPG may be an important mediator especially in elderly RA cases.



## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with polyarticular synovitis. It is characterized with the breakdown of cartilage, juxta-articular bone, and generalized bone loss with reduced bone mass. The consequences of this intense bone loss are painful joint deformities, progressive functional disability, and increased risk of bone fractures and increased mortality rates [1].

Receptor activator of nuclear factor κB ligand (RANKL) that belongs to the TNF superfamily, exists as a soluble form (sRANKL) [2,3]. Receptor activator of nuclear factor κB ligand, expressed on osteoclasts/stromal lineage cells, plays a stimulating role to transduce differentiation and send activation signals to osteoclast lineage cells through binding to its receptor (RANK) which leads to osteoclastogenesis and bone resorption in patients with RA [1,3]. Osteoprotegerin (OPG) is produced by osteoblasts and it is an important regulator of osteoclast development and function. Osteoprotegerin acts as a decoy receptor by blocking RANKL–RANK binding preventing osteoclastogenesis and bone resorption [4,5]. Its overexpression acts as a consequence of inhibition of osteoclast production and can cause osteoporosis in mice, while OPG deletion leads to an increase in remodeling of bone and osteoporosis [6,7]. Thus, expression of RANKL and OPG give rise to controlling RANK activation and balance between OPG and RANKL levels; meanwhile, OPG plays fundamental roles in order to determine the extent of bone resorption [8–10]. Previous studies reveal that disequilibrium of RANKL and OPG together may indicate relatively skeletal complications as well as deregulations of this system implicate the pathophysiology of bone remodeling in patients with RA [11–13].

Several experiments clearly show the role of RANKL in inflammatory joint disease in laboratory animal models. Activated T cells in vivo culminate in RANKL-mediated increase in osteoclastogenesis and bone loss [14–16]. In RA, it has been confirmed that T-cell activation could cause osteoclastogenesis within the synovium and this can be conducted via two mechanisms: (A) Secretion of RANKL by active T cells in inflamed joints. (B) Increasing bone erosions. On the contrary, OPG probably contributes to preventing inflammation-induced bone resorption in RA patients [17]. Administration of OPG to animals with arthritis blocks bone demolition; however, with less influence on inflammation [18]. Serum OPG concentrations are also elevated in RA patients [19]. OPG is an effective inhibitor for differentiation of osteoclasts and could prevent bone resorption in patients with RA [20]. Some evidences suggest that the balance between OPG and RANKL is important in prevention of joint destruction [21,22] and therefore, data suggest that inhibition of RANKL function via OPG plays a protective role to bone destruction in RA patients [23].

Vascular calcification (VC) is known to be associated with a high risk of coronary atherosclerosis morbidity and mortality in RA patients [24]. Matrix Gla protein (MGP) is among the most important inhibitors of VC [11,25]. Its effect on VC is mediated by inhibiting of calcium crystal formation, with binding surplus calcium ions or small crystals in tissues and clearing them from circulation [26,27]. Data demonstrate that serum MGP concentrations in patients with calcification were lower in comparison to patients without calcification [28,29]. Herrmann et al. [30] reported a significant decrease in serum MGP level with increased severity of coronary calcification. Moe et al. [31] believe that OPG and MGP may protect against VC in the uremic patients. Nevertheless studies including correlations between serum OPG and MGP levels and disease activity score including C-reactive protein (DAS28-CRP) in patients with RA have not yet been reported.

The aim of the present study was to evaluate serum MGP and OPG levels in female Rheumatoid Arthritis (RA) patients and study their relation to the disease activity.

## 2. Patients and methods

Forty-five women aged 46.5 ± 12.6 years affected by RA (Disease duration: 1–22 years) were compared with 45 healthy age, sex and body mass index (BMI) matched controls (43.2 ± 9.2 years). The median and range of the age was 48 (21–69) years in the RA group and 41(21–62) years in the healthy control group ($p = 0.2$). Patients were selected consecutively from the Rheumatology Clinic of Tabriz University of Medical Sciences (RCTUMS) between August 2010 and Jan 2011 and were enrolled into the study according to the ACR/EULAR 2010 classification criteria of RA [32]. Before investigation, written informed consent was obtained from all participants. Exclusion criteria in the present study were patients with history of smoking or alcoholism, renal disease, cardiovascular and liver inheritance systemic disease, uncontrolled hypertension, nephrotic syndrome, diabetes mellitus, Cushing syndrome, thyroid disorders, anti-conception drugs and metabolic diseases. The patients with changed drug treatment schedule in the previous two months and during the