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# Evaluation Of The Relationship between Serum Uric Acid and Bone Mineral Density In Rheumatoid Arthritis Male Patients

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## ABSTRACT

**Background:** Hyperuricemia is a common risk factor for conditions associated with oxidative stress. Alternatively, there is increasing evidence that normal serum uric acid (UA) plays a protective role as an antioxidant. Osteoporosis was commonly attributed to oxidative stress and is a common complication of rheumatoid arthritis (RA).

**Objectives:** To study the relationship between serum UA and bone mineral density in male patients with rheumatoid arthritis.

**Patients and methods:** Fifty RA male patients were included in this study. Age, disease duration, and type of medication were recorded. Clinical examination for tender and swollen joints was done and disease activity score 28 was calculated. Body mass index, random blood glucose, erythrocyte sedimentation rate, C-reactive protein, serum UA, rheumatoid factor and anti-CCP were measured. Bone mineral density was measured using dual-energy X-ray absorptiometry at the lumbar spine, hip and radius.

**Results:** A highly significant positive correlation between serum UA and T scores in the lumbar spine and hip. However, serum UA was negatively correlated with disease activity, ESR and CRP ($P < 0.001$). There was significant ($P < 0.001$) association between serum UA and different therapeutic agents (levels of serum UA were higher in patients taking combined biological and conventional disease modifying anti-rheumatic drugs (DMARDs) than those who were taking biological or conventional DMARDs alone.

**Conclusion:** High normal serum UA level is protective against osteoporosis at both the lumbar spine and hip in male rheumatoid arthritis patients. Also, serum UA level is negatively correlated with RA disease activity and acute phase reactants in male patients with RA.

**Keywords:** Rheumatoid Arthritis, uric acid, DMARDs, DAS28, DEXA.

## INTRODUCTION

Purine metabolism in humans is a complex process. Its final steps are catalyzed by the enzyme xanthine oxyreductase and the end product of this process is uric acid (UA). Uric acid production is related to the release of reactive oxygen products. That's why there had been epidemiological evidence that hyperuricemia is a risk factor for conditions associated with oxidative stress, such as cardiovascular diseases, metabolic syndrome, and chronic kidney diseases [(1)]. Alternatively, there is an increasing clinical evidence that serum UA, while within the normal range, has anti-inflammatory and anti-oxidative effects, and plays a protective role as an antioxidant [(2)].

People with rheumatoid arthritis (RA) have progressive joint damage, functional impairment, and numerous extra-joint complications. In addition to bone loss around the localized joint, osteoporosis is a common complication of RA [(3)]. Osteoporosis was commonly attributed to oxidative stress [(4)]. The effect of UA on generalized bone loss is gaining more importance. Many observational studies revealed an association between a high normal serum UA level and bone mineral density (BMD). Therefore, a lower risk of osteoporosis and fragility fractures in post-menopausal women was associated with high normal serum UA levels. This indicated that UA exerts a protective effect against bone loss [(5)].

The positive correlation between serum UA levels and bone mineral density has frequently been reported in the normal population and in post-menopausal females [(2,3,5)]. However, there are little data regarding the effect of serum UA levels on bone loss in male patients with rheumatoid arthritis. We aimed to study the relationship between serum UA level and bone mineral density in male patients with RA.

## PATIENTS AND METHODS

This cross-sectional study included fifty male patients with rheumatoid arthritis diagnosed according to **ACR/EULAR criteria (2010)**[(6)]. They were recruited from the Outpatient Clinic of Rheumatology, Physical Medicine and Rehabilitation Department in our hospital during the period between July 2020 to December 2020.

### Ethical approval:

**The study protocol was approved by the Local Ethics Committee of Faculty of Medicine, Menofia University and in line with the World Medical Association Declaration of Helsinki,** and informed consent was obtained from all patients.





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**The exclusion criteria:**

Patients with body mass index higher than 25. Patients with diabetes or who has hyperuricemia, gout, urinary stones or receiving hypouricemic drugs. Patients underwent spine or hip surgery or have metal implants in situ that affect the BMD evaluation. Patients taking medications such as bisphosphonates, teriparatide, or denosumab (except calcium and vitamin D).

For all patients, age, body mass index (BMI), disease duration, and types of disease modifying anti-rheumatic drugs (DMARDs) used for treatment were recorded. Clinical joint examination was performed for tender and swollen joints. Laboratory investigations included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum uric acid (UA), random blood glucose, rheumatoid factor (RF), and anti-cyclic citrullinated peptide antibody (anti-CCP). Dual-energy X-ray absorptiometry scan was done (using Osteo Prima DEXA bone densitometer / pencil beam, Korea) for detection of osteoporosis in the lumbar spine, hip and left radius. T- scores were used, and a diagnosis of osteoporosis made for T-scores of -2.5 or less (male reference database) in men aged 65 years and older and in men from 50 to 64 years of age if other risk factors for fracture are present [(7)].

Rheumatoid arthritis disease activity score was assessed using the 28-joint count for swelling and tenderness with ESR disease activity score (DAS28-ESR) online calculator. The disease activity was classified into 4 groups as follows- high disease activity was defined as DAS28-ESR of > 5.1, moderate disease activity was defined as ($3.2 < DAS28\text{-}ESR \leq 5.1$), low disease activity was defined as ($2.6 < DAS28\text{-}ESR \leq 3.2$), and remission was defined as $DAS28\text{-}ESR \leq 2.6$ [(8)].

**Sample size estimation:**

A pilot study was conducted on 10 rheumatoid arthritis (RA) male patients. Uric acid and bone mineral density were measured, correlation between uric acid and bone mineral density was +0.39, at alpha error 0.05 and power of the study 80% , the calculated sample was 50 RA cases.

***Statistical analysis***

Data were collected, tabulated, statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 22 (SPSS.inc, Chicago, Illinois) where the following statistics were applied: Descriptive statistics in which quantitative data were presented in the form of mean ( $\overline{X}$), standard deviation (SD), and range. Qualitative data were presented in the form of numbers and percentages (%). Analytical statistics, Spearman correlation coefficient test (r-test) was used to study the correlation between non-parametric quantitative variables. Statistical significance at $p \leq 0.05$.

**RESULTS**

Our study showed that patients' age ranged from 52 to 75 years with a mean of 63.50 ± 10.50, disease duration ranged from 5–16 years with a mean of 6.45 ± 4.01. The mean BMI of the study group was 21.86 ± 2.86. Number of tender points of the patients ranged from 0–10 with mean 3.72 ± 2.75, number of swollen joints ranged from 0-14 with a mean of 3.22 ± 3.22. Regarding DAS28, 4 patients were in remission, 13 patients had low disease activity, and 33 patients had moderate activity while 10 patients were in high disease activity (Table 1).

**Table (1):** Demographic and clinical characteristics of the studied patients

| | **Study Group (n=50)** | |
|---|---|---|
| | **Mean ± SD Range** | |
| **Age (years)** | 63.50 ± 10.50<br>52.0 - 75.0 | |
| **Disease duration (years)** | 6.45 ± 1.4<br>0.5 - 16.0 | |
| **BMI (kg/m$^2$)** | 21.86 ± 2.86<br>19.0 - 24.72 | |
| **Number of tender joints** | 3.72 ± 2.75<br>0.0 - 10.0 | |
| **Number of swollen joints** | 3.22 ± 0.78<br>0.0 - 14.0 | |
| **Disease activity (DAS 28)** | 4.46 ± 1.14<br>1.89 - 6.88 | |
| **Disease activity (DAS 28)** | **No.** | **(%)** |
| Remission | 4 | 8.0 |
| Low | 3 | 6.0 |
| Moderate | 33 | 66.0 |
| High | 10 | 20.0 |
| **Medication used** | | |
| Conventional DMARD | 25 | 50.0 |
| Biological DMARD | 17 | 34.0 |
| Combined | 8 | 16.0 |

**SD:** standard deviation, **BMI**: body mass index, **DAS:** disease activity score, **DMARD**: disease modifying anti-rheumatic drugs.

Twenty-five patients (50%) were taking conventional DMARDs while 17 patients (34%) were taking a tumor necrosis factor (TNF) inhibitors as biological therapy and 8 patients (16%) were receiving combination of biological therapy and conventional DMARDs. ESR in the first hour ranged from 10–70 mm/hour with a mean of 41.24 ± 18.26, serum UA ranged from 3-6 mg/dl with a mean of 5.0 ± 1.16 and random blood glucose mean was 132.78 ± 36.26mg/dl. CRP was positive in 76% of the patients

while 24% were negative. Rheumatoid factor was positive in 86% of patients while 82% had positive anti-CCP. The mean T-score at lumbar spine and hip were in the range of osteopenia (-2.44 and – 1.28 respectively). 80% of patients had osteopenia at the lumbar spine and T-score ranged from 0.9 to -4.1 with a mean of - 2.44 ± 1.05. In the hip 74% of patients had osteopenia and T score ranged from - 3.1 to 1.2 with a mean of - 1.28 ± 1.14, while in the distal radius T score ranged from - 3.2 to 0.7 with a mean of - 0.98 ± 1.20 (Table 2).

**Table (2):** Laboratory and DEXA scan results of the studied patients

| | **Study Group (n=50)** | |
|---|---|---|
| | **Mean ± SD** | |
| **ESR (first hour).** | 41.24 ± 8.26 | |
| **Serum uric acid (mg/dl).** | 5.0 ± 1.16 | |
| **Random blood glucose (mg/dl).** | 132.78 ± 6.26 | |
| **CRP (mg/dl).** | 15.16 ± 1.43 | |
| **CRP:** | **No.** | **(%)** |
| Positive | 38 | 76.0 |
| Negative | 12 | 24.0 |
| **Rheumatoid factor** | | |
| Positive | 43 | 86.0 |
| Negative | 7 | 14.0 |
| **Anti CCP** | | |
| Positive | 41 | 82.0 |
| Negative | 9 | 18.0 |
| **DEXA (lumbar T)** | - 2.44 ± 0.05 | |
| **DEXA (hip T)** | - 1.28 ± 0.14 | |
| **DEXA (radius T)** | - 0.98 ± 0.20 | |

**SD:** standard deviation, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **ACCP:** anti-cyclic citrullinated peptide, **DEXA:** dual energy X ray absorbiometry.

Results showed that there was highly significant positive correlation between serum uric acid and DEXA parameters regarding T scores in the lumbar spine and hip while serum uric acid was negatively correlated with disease activity (DAS28), ESR and CRP (P value < 0.001). Non-significant positive correlation was found between serum UA and T-score at radius, random blood glucose and BMI (Table 3).

**Table (3):** Correlation between serum uric acid and DEXA scan T score, DAS28, and laboratory measures of the studied group

| | **Serum uric acid of study Group (n=50)** | |
|---|---|---|
| | **r** | **P value** |
| DEXA (lumbar T) | 0.80 | <0.001 **HS** |
| DEXA (hip T) | 0.47 | 0.001 **HS** |
| DEXA (radius T) | 0.10 | 0.47 NS |
| Disease activity (DAS 28) | - 0.51 | <0.001 **HS** |
| ESR | - 0.49 | <0.001 **HS** |
| CRP | - 0.68 | <0.001 **HS** |
| BMI | 0.09 | 0.52 NS |
| RBG | 0.05 | 0.69 NS |

**r :** spearman correlation, **DEXA:** dual energy X-ray absorbiometry, **DAS:** disease activity score, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **BMI:** body mass index, **RBG:** random blood glucose, **HS:** highly significant, **S:** significant, **NS:** non-significant.

Also we found a highly significant association between elevated serum UA and normal DEXA scan T-score at both lumbar spine and hip (Table 4).
Results showed that there was highly significant (P < 0.001) association between serum uric acid and different types of medications (levels of serum uric acid were higher in patients taking combined biological and conventional DMARDs (5.75 ± 0.46) than those who were taking biological DMARDs only (5.53 ± 1.0) or conventional DMARDs only (4.40 ± 1.11) (Figure 1).

**Table (4):** Association between serum uric acid and medications and DEXA scan T score of the studied group

| | Serum uric acid of study Group (n = 50) | Test of sig. | P value عذ |
|---|---|---|---|
| | Mean ± SD | | |
| **Medication used:**<br>Conventional DMARD<br>Biological DMARD<br>Combined | <br>4.40 ±1.11<br>5.53 ± 1.0<br>5.75 ± 0.46 | 8.99 | < 0.001<br>**HS** |
| **DEXA (lumbar T)**<br>Normal (n=10)<br>osteopenia (n=40) | <br>6.0 ± 0.23<br>4.75 ±1.17 | 6.75 | <0.001<br>**HS** |
| **DEXA (hip T)**<br>Normal (n=13)<br>osteopenia (n=37) | <br>5.69 ± 0.85<br>4.76 ± 1.16 | 3.07 | 0.005<br>**S** |
| **DEXA (radius T)**<br>Normal (n=25)<br>osteopenia (n=25) | <br>5.24 ± 1.16<br>4.76 ± 1.12 | 1.48 | 0.14<br>NS |

**DEXA:** dual energy X ray absorbiometry, **DMARD:** disease modifying anti-rheumatic drugs, **HS:** highly significant, **S:** significant, **NS:** non-significant.

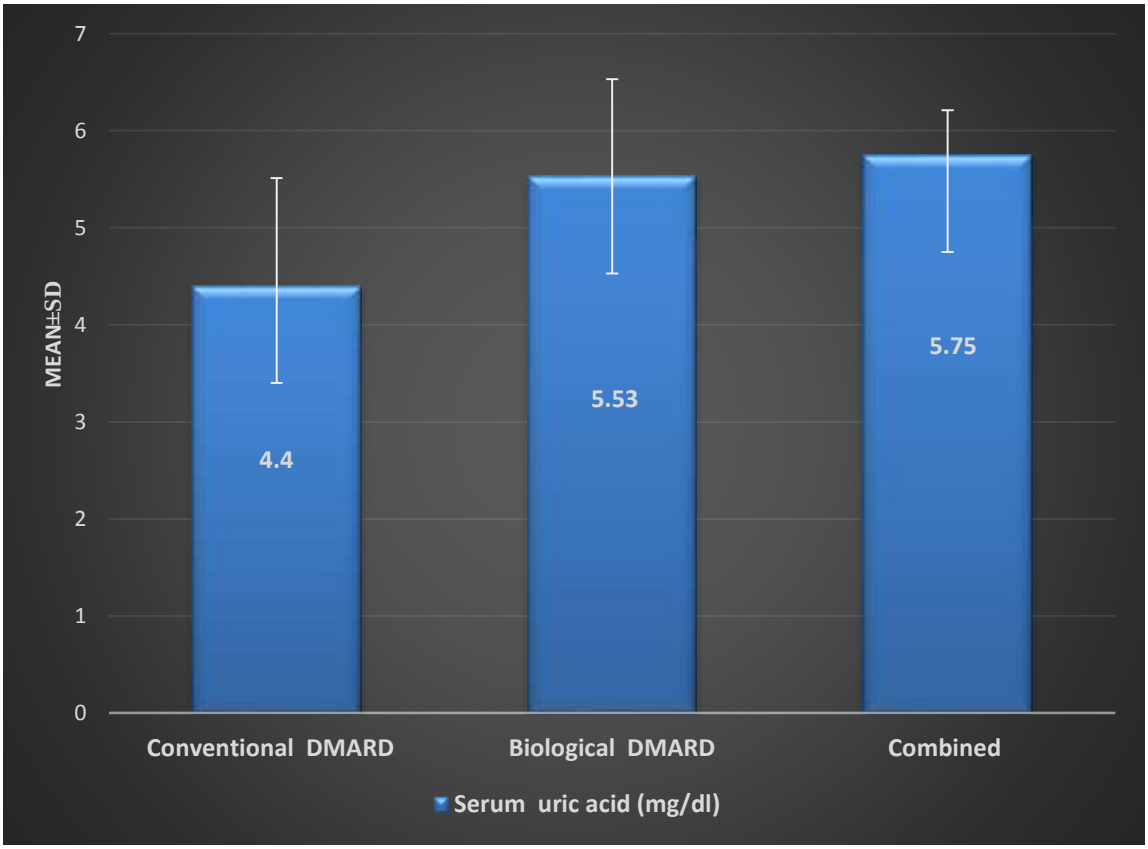


**Figure (1):** Association between serum uric acid and medications of the studied group

## DISCUSSION

Because of its high prevalence, osteoporosis is considered a serious complication in patients with rheumatoid arthritis. As female gender is a common risk factor for osteoporosis, many studies have investigated the association between serum uric acid levels and bone mineral density in postmenopausal women with RA; however, few studies investigated this relation in RA male patients. In this study, we included fifty male patients with rheumatoid arthritis, and we studied the relation between serum UA level and bone mineral density and RA clinical and laboratory parameters.

The measurement of bone mineral density using DEXA scan revealed that the mean T score at lumbar spine and hip were in the range of osteopenia (-2.44 and – 1.28 respectively). As all patients were rheumatoid arthritis patients, this was an expected result. **Kweon *et al.* [9]** reported a similar result that lumbar spine or hip osteoporosis among male patients with RA was significantly more than that among controls (22.4% vs 10.5%, *P* = .049)**.**

Our study revealed that there were highly significant positive correlations between serum uric acid and DEXA scan T-scores at both lumbar spine and hip ( r = 0.80 P <0.001, r = 0.47 P= 0.001 respectively) while there was non-significant positive correlation with T score at the radius. Also, a highly significant association was found between high normal serum uric acid and normal BMD at both lumbar spine and hip (P < 0.001 and P =0.005 respectively).

Bone mineral density at both the lumbar spine and hip was significantly associated with high normal serum UA levels as reported in many previous studies. As **Nabipour *et al.* [10]** study on normal males, which revealed that above-median serum UA levels were related to a reduced prevalence of osteoporosis at the femoral neck (p = .010) and lumbar spine (p = .016)**.** Also, **Lee *et al.* [2]** reported that serum UA concentration was positively correlated with BMD at lumbar spine (P=.032), femoral neck (P=.01), and total hip (P=.002) in postmenopausal RA females**.** Similar result was reported by **Sritara *et al.* [11]** in normal older males at the lumbar spine (p < 0.05)**.**

Regarding another autoimmune disease complicated by osteoporosis, ankylosing spondylitis, **Kang *et al.* [12]** found that lower serum UA levels were associated with lower BMD in young male patients**.**

In this study, we found that RA disease activity using the mean DAS 28(ESR) score was 4.46 and there was a highly significant negative correlation between serum uric acid level and DAS 28, ESR, and CRP level. This could be explained by the long disease duration and that our patients were already on DMARDs which control the disease activity and at the same time has great effect on level of serum uric acid. Alternatively, **Ghosh *et al.* [13]** found a positive correlation between serum UA and clinical disease activity index and hs-CRP with extremely high statistical significance in 120 newly diagnosed DMARD naive RA patients of them 36 patients were males**.**

We also found a highly significant association between serum UA and different types of medications used; either conventional DMARDS, biological DMARDS, or combined therapy with higher serum uric acid levels in patients using biological or combiner therapy and lower level in patients using conventional DMARDS only. This is in agreement with the data reported from previous studies as **Lee *et al.* [14]** who reported that serum UA decreases during taking methotrexate therapy for RA and the patients had better clinical outcomes at 18 months by reaching a DAS (ESR)28 defined remission and an SJC28 score of <1**. Also, Choe and his colleagues [15]** confirmed that leflunomide therapy for RA resulted in reduction of serum uric acid via enhancing the urinary excretion of UA. **Hasikova *et al.* [16]** studied 128 patients with clinically and serologically highly active systemic autoimmune rheumatic diseases (SARDs) of them 44 patients with RA and noticed the significant increase in serum UA after 3 months of treatment with TNF inhibitors (p < 0.0001), and male sex was an important predictor of ΔSUA in univariate and multivariate models**.**

Further studies on large number of patients and healthy controls are necessary for further confirmation and refining of our results.

## CONCLUSION

Based on the demonstrated results, we could conclude that in male patients with RA above 50 years old, there was an increased prevalence of reduced bone mineral density. In addition, high normal serum UA level is associated with increase in bone mineral density. Moreover, serum UA level is negatively correlated with RA disease activity and acute phase reactants in male patients with RA. The use of biological DMARDS (TNF inhibitors) was significantly associated with high normal serum UA levels.

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