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Bone Mineral Density in Iranian Female patients with Rheumatoid Arthritis.

Zakeri Z*, Sandooghi M*, Mashhadi MA**.

* Assistant Professor, Section of Rheumatology, Department of Internal Medicine,
**Associate Professor, Section of Hematology and Oncology, Department of Internal Medicine, Hematology Oncology Research Center, Zahedan University of Medical Science, Zahedan, Iran.

Correspondence: Dr. Z. Zakeri, Department of Internal Medicine, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran, Telephone: +98(911) 5141-0570 E-mail: zah_zakeri@yahoo.com

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Abstract:

Background: Patients with rheumatoid arthritis (RA) are at increased risk of developing low bone mineral density. The aim of the present study was to compare the bone mineral density of Iranian female RA patients with healthy controls.
Materials and methods: In this case-control study, bone mineral density of 391 rheumatoid arthritis patients and 391 healthy controls referred during a 4-year period (2003-2007) to Imam Khomeini Hospital in Tehran, were studied. Patients were assigned in two subgroups; group 1 (n=184) with a history of current oral corticosteroid use and group 2 (n=207) without corticosteroid use. Dual-energy x-ray absorptiometry technique was used to measure bone density. Differences between groups were analyzed using Fisher's exact test. Duncan test and Schaffer test were used to compare mean difference between each two groups.
Results: Among ≤45 and >60 years females, bone density did not show a significant difference at lumbar region between the 3 groups, however, the differences at femoral neck were statistically significant ($p<0.04$ for ≤45 years and $p<0.0003$ for >60 years). Among subjects aged 46-60 years, bone mineral density showed significant differences at both lumbar and femoral neck regions ($p<0.001$, $p<0.001$, respectively).
Conclusion: Low bone density in Iranian female patients with RA is in accordance with western societies. Among RA female patients the risk of BMD reduction is increased by age and partly by oral glucocorticoids. Therefore, routine BMD evaluation is strongly suggested for RA patients.

Keywords: Rheumatoid arthritis, Bone mineral density, Female, Glucocorticoid.

Introduction:

There has been a growing awareness that patients with rheumatoid arthritis (RA) are at increased risk for decreased bone density compared with healthy controls. Several studies have demonstrated a decrease in bone mineral density (BMD) in patients with RA.[1-3] A reduction in bone mineral density is associated with increased bone fragility and risk of fracture, with osteopenia and osteoporosis carrying a twofold and four- to five-fold increase in risk of fracture, respectively.[1,4]

Although the exact pathogenesis for the lower BMD in RA patients has not been clearly understood, a number of factors have been implicated. Prior studies have postulated several predisposing factors such as age, sex, height, weight, parity, time since the menopause, corticosteroid therapy, calcium and vitamin D deficiency, sex-hormone deficiency, malnutrition, smoking, inflammatory cytokines, and physical inactivity, however, study results have not been consistent.[5,6] In addition, several factors specifically related to RA could also be important. Most often the duration of the disease, the degree of functional impairment, and the severity of the inflammatory process have been suggested as potential risk factors for osteoporosis in patients with RA.[5] The chronic inflammation associated with RA has been shown to be an important risk factor in the development of systemic osteoporosis.[7] However, the mediator mechanisms and the link between the local arthritic process and systemic bone loss are still unclear. Moreover, RA sometimes requires long-term treatment with glucocorticoids that may lead to many well-known adverse events.[1,8]

The aim of the present study was to compare the bone mineral density of Iranian female RA patients with healthy controls on the base of age in three age group: <45,46-60 & >60 years. as well as determining the corticosteroid use as a risk factor for low BMD in RA patients.

Materials and Methods:

In this case-control study, bone mineral density of a total of 782 subjects referred during a 4-year period (2003-2007) to Imam Khomeini Hospital in Tehran, were studied. They were assigned in 2 groups of case (391 rheumatoid arthritis patients) and control (391 healthy controls). All patients were Iranian women who had met the diagnostic criteria of the American College of Rheumatology revised in 1998.[9] The following exclusion criteria were applied at baseline: ileal resection, chronic liver or renal failure, abnormal thyroid or parathyroid function, diabetes, malignancy, hypogonadism, and any other known bone disorder other than osteoporosis or osteopenia. Those who might be pregnant during the study period were excluded.

Patients were assigned in two subgroups: The first group (group 1) consisted of 184 patients with RA and a history of oral corticosteroid use (ever-users) at a dose of at least 5mg daily for a period of at least 3 months; the second group (group 2) included 207 patients with RA who had never received corticosteroid (non-users). Meanwhile, the control group (group 3) was compromised of 391 normal controls with neither RA nor a history of corticosteroid consumption, recruited

from subjects who present to gynecology clinic for periodic examination.

A single operator used Lunar DPX-IQ (DXA; Lunar Radiation Corp., Madison, USA) scanner to obtain dual-energy x-ray absorptiometry (DXA) measurements of lumbar spine in the anterioposterior projection (L2-L4) and femoral neck using the standard protocols. Data were reported based on bone mineral content gr/cm2. The coefficients of variation of the bone mineral measurements in all sites were less than 2%.

The study protocol was approved by the Ethical Committee of the Medical University of Iran. Having our goal explained, patients were asked to complete an informed consent. There was the possibility of interrupting the patient's cooperation, as he/she desired.

Results are expressed as mean ± standard deviation (SD) for continuous variables, unless otherwise stated. Differences between groups were analyzed using Fisher's exact test, when appropriate. Duncan test and Schaffer test were used to compare mean difference between each two groups. Two-tailed significance tests were used in all statistical analyses. For all tests, significance level was defined as $p<0.05$ (95% confidence interval). All statistical analyses were achieved using SPSS software (SPSS version 11.5, USA).

Results:

The mean age (±standard deviation) of RA females on steroids was 55±9 years, while it was 52±10 years for steroid-free RA females. The mean age of controls was 53±10 years. The age differences between groups did not reach a statistically significant level.

Subjects were classified in 3 groups of ≤45, 46-60, and >60 years, however, in all groups, most of the subjects aged between 46-60 years.

Table 1 represents bone mineral density of all females at lumbar spine region. Among age groups under 45 yrs, there was no significant difference (NS), however, Duncan test revealed significant difference between RA patients on steroid (Group 1) and control group (Group 3) ($p<0.05$).

Among subjects aged 46-60 years, bone mineral density of lumbar spine showed significant differences ($p<0.001$). Duncan test revealed significant differences between group 1 and either group 2 or 3 ($p<0.05$), however, controls were not significantly differed from steroid-free RA patients.

Among females older than 60 years, there was no significant difference between 3 groups. Furthermore, each two groups failed to show a significant difference (table 1).

Table 1- Bone mineral density (gr/cm2) at lumbar spine of study population according to the age group

Age group (yrs)	Steroid ever-user RA patients (group1) (n =184)	Steroid-free RA patients (group 2) (n =207)	Control (n =391)	P
≤45	1.09±0.15 (1.04-1.15)*	1.11±0.16 (1.06-1.17)	1.11±0.15 (1.08-1.14)	0.86
46-60	0.98±0.17 (0.94-1.03)	1.01±0.19 (0.98-1.05)	1.09±0.16 (1.07-1.11)	<0.0001
>60	0.89±0.18 (0.84-0.93)	0.88±0.19 (0.84-0.93)	0.94±0.14 (0.90-0.98)	0.18

* 95% Confidence interval

Totally, bone mineral density at lumbar region was lower in RA patients on steroid followed by steroid-free RA patients and controls.

Table 2 represents bone mineral density of all females at femoral neck.

Among ≤45 years females, there was significant differences between 3 groups ($p<0.04$), nevertheless, Duncan test revealed significant difference between group 1 and 3 ($p<0.05$) (table 2).

In 46-60 years age group there was significant differences between 3 groups ($p<0.001$), while there was significant differences between either of two groups, separately (table 2).

Among subjects older than 60 years, there was significant differences between 3 groups ($p<0.001$) and Duncan test showed significant difference between group 1 and either of group 2 or 3 ($P<0.05$) (table 2).

Similarly, bone mineral density at femoral neck was lower in RA patients on steroids followed by steroid-free patients and controls. Meanwhile, bone mineral density of femoral neck was lower than lumbar spine, especially in RA patients on steroids.

Table 2 -Bone mineral density(gr/cm2) at femoral neck of study population according to the age groups

Age group (yrs)	Steroid ever-user RA patients (group1) (n =184)	Steroid -free RA patients (group 2) (n =207)	Control (n =391)	P
≤45	0.84±0.15 (0.79-0.89)	0.86±0.14 (0.81-0.90)	0.90±0.12 (0.87-0.93)	0.04
46-60	0.78±0.14 (0.74-0.81)	0.82±0.13 (0.79-0.85)	0.88±0.12 (0.86-0.89)	<0.0001
>60	0.68±0.12 (0.65-0.71)	0.68±0.11 (0.65-0.71)	0.76±0.09 (0.73-0.78)	<0.0003

*95% Confidence interval

Discussion:

The present study shows that bone mineral density is reduced in patients with RA on steroids especially in older age. The loss of cortical bone in RA may be partly attributed to the relative immobility of a painful article, which characteristically produces the radiological sign of periarticular osteoporosis largely as a result of bone resorption. Hence, bone density may also reflect disease activity to a degree.

In this study, patients on steroid therapy had more reduction in bone mineral density than healthy control subjects and steroid-free patients. The influence of oral steroid therapy on BMD was profound. Although corticosteroids are known to reduce bone density within several weeks of starting treatment, trabecular bone is affected before cortical bone loss occurs.[1,10] We didn't explore the effect of steroid dosage on the degree of BMD, but others have suggested that much of the bone loss caused by steroids occurs early in treatment [11,12], is dose related [13] and partially reversible on stopping therapy.[14] Alternative forms

of administration of corticosteroids appear not to induce significant bone loss [15,16] and may be preferable to oral steroid therapy. De Nijs et al reported that the prevalence of vertebral fractures is more than doubled in RA patients currently taking oral steroids and that steroid consumption remains highly significant after correcting for disease duration and activity.[17] In a Southampton, UK case-control study, the effects of RA and oral glucocorticoids were found to be largely independent of each other; patients with RA who were not receiving oral glucocorticoids had a double risk of hip fracture, although this did not reach statistical difference.[18] however in this research we didn't study the total dos of steroid consumption in each of users but these patients recived 5-10 mg daily prednisolon overall.

We found that in all groups, bone mineral density reduced with increasing age. It is known that increased age especially postmenopausal women are at risk of osteoporosis. On the other hand, rheumatoid arthritis and glucocorticoids worsen the reduction of BMD and enhance development of osteoporosis.

Our study has several limitations. Unfortunately we studied only female patients and we didn't consider duration of disease in RA patients, dosage and duration of glucocorticoids use, disease activity and some risk factors of BMD osteoporosis.

In conclusion, this study demonstrated that patients with RA have an increased risk of BMD reduction of femoral neck in all age groups and in 46-60 years age group patient in lumbar spine. The increased risk is attributable partly to use of oral glucocorticoids.

Interestingly in 46-60 years age group controls were not significantly differed from steroid-free RA patients. this maybe related to either not using steroid or milder disease and no need to glucocorticoids consumption.

Conflicts of interest:

There was no potential financial conflict of interest before or during the study process.

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