The usefulness of osteocalcin measurements in Malaysian patients with rheumatoid arthritis

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Objective: Rheumatoid arthritis (RA) is a chronic inflammatory condition that can be associated with abnormal bone turnover and hence osteoporosis. Osteocalcin (OC) levels are increased in conditions with high bone turnover, including high RA disease activity. Thus, OC levels could possibly be used as a marker to assess bone health and disease activity in RA patients. As there have been no previous studies looking at serum OC levels in Malaysian RA patients, this study was performed to examine possible correlations between OC, bone mineral density (BMD) and disease activity in this population.

Methods: A cross-sectional study of 75 female RA patients and 29 healthy controls was performed. Serum OC was measured using a Quantikine® ELISA kit. Dual-energy x-ray absorptiometry (DXA) was used to assess BMD.

Results: Serum OC levels were not significantly different between RA patients (median 14.44 ng/mL, interquartile range [IQR 12.99]) compared to healthy controls (median 11.04 ng/mL IQR 12.29) (p=0.198). Serum OC increased with age (Spearman's rho r=0.230, p=0.047). There was no significant correlation between serum OC and body mass index (BMI), menopause status, BMD, DAS28, swollen or tender joint counts. Overall, there were 11 (14.7%) patients with osteoporosis and 27 (36.0%) with osteopenia. Menopause status was significantly associated with BMD at all sites (lumbar spine p=0.002, femoral neck p=0.004, total hip p=0.002).

Conclusions: Serum OC were similar in RA patients compared to healthy controls. In RA patients, serum OC did not correlate with RA disease activity or BMD. Menopause status remains an important influence on BMD. Thus, measuring serum OC levels in Malaysian RA patients was not useful in identifying those at risk of low BMD.

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Introduction

Bone turnover markers measure proteins released during bone formation and degradation products produced during bone resorption. Osteocalcin (OC) is one of these bone turnover markers; it is a small protein of 49 amino acids produced by mature osteoblasts, odontoblasts and hypertrophic chondrocytes and is regarded as a specific marker of osteoblast function, as its levels correlate with bone formation. Levels of OC are also increased in diseases with high bone turnover. Bone turnover markers have been studied extensively in osteoporosis and currently, it is not recommended that they are used as a method to diagnose osteoporosis. However, they can be useful in monitoring individual patients with osteoporosis being treated with anti-resorptive medications and be used as an additional factor in fracture risk assessment.[1]

In patients with rheumatoid arthritis (RA), there is both peri-articular osteopeniaas well as generalised osteoporosis.[2] However, despite the presence of generally lower bone mineral density (BMD) in RA patients, serum OC levels in RA have not been shown to correlate with BMD.[3,4] Levels of OC in RA patients have been shown to be both higher[5], lower[6] or the same[7] when compared to healthy controls. The joint inflammation that occurs in RA patients would be another reason for the presence of increased bone turnover. Previous studies looking at serum OC and RA disease activity have been contradictory. Serum OC levels have been shown to be higher[8] or lower[9] in those with active disease as well as being no different between active and mild disease.[4,6,10]

Thus, changes in serum OC levels can reflect bone health and/or may be altered in patients with RA depending on their disease activity. As there have been no previous studies looking at serum OC levels in Malaysian RA patients, this study was performed to examine possible correlations between serum OC, BMD and RA disease activity in this population, to determine if OC levels could be useful in the assessment of bone health.

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Methods

Subjects

This was a cross-sectional study where consecutive patients with RA, aged between 40 and 90 years, without any of the exclusion criteria, were approached and recruited from the rheumatology clinic at Hospital Tuanku Jaafar, Seremban, and Klinik Pakar Puchong, Puchong, during the period July 2014 to March 2015. Healthy control subjects of similar ages were recruited from hospital or clinic staff and their relatives or friends.

RA patients were eligible for the study if they fulfilled the 1987 classification criteria for those diagnosed before 2011[11], and the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria had to be fulfilled for those diagnosed from 2011 onwards.[12] Patients were excluded if they already had a fracture, or were known to have osteoporosis, or were on any treatment for osteoporosis, or had renal impairment (serum creatinine > 115 μmol/L), known or past metabolic bone disorders, malabsorption, thyroid disease, immobilisation, or taking other drugs which affected bone homeostasis (e.g. phenytoin, cyclosporine, oral contraceptive pill). As this was a study on RA patients, we allowed the current use of low-dose corticosteroids (prednisolone < 7.5 mg daily) and oral methotrexate.

RA disease activity was assessed by DAS28, a disease activity score calculated based on assessments of 28 tender and 28 swollen joints, the erythrocyte sedimentation rate and patients' global assessments of their health on a 10 cm visual analogue scale.[13]

Bone mineral density measurement

Bone mineral density (BMD) of the lumbar spine [LS] [L2–L4] and left hip (femoral neck [FN] and total hip [TH]) were measured by dual-energy X-ray absorptiometry (DXA) with a HOLOGIC Discovery W densitometer (Hologic Corporation, Bedford, MA, USA) at both sites. The precision of the machine is ± 1%. The reference population used was the machine manufacturer's female Japanese population database. BMD was classified into normal, osteopenia and osteoporosis based on T-scores as defined by the World Health Organisation.[14]

Biochemical analysis

All blood samples were taken in the morning. Three millilitres of blood were withdrawn from each subject, using a Vacutainer® into an EDTA tube, and chilled to 4°C until processing. The blood was then centrifuged for 15 minutes at 1,000 g, the supernatant serum was removed, aliquoted and stored at -20°C until use. Osteocalcin in these patients' sera was measured using the Human Osteocalcin Quantikine® ELISA kit (R&D Systems, USA). The intra-assay precision coefficients of variation (CV) ranged from 1.6–3.4% and inter-assay precision CV ranged from 4.9–9.7%.

Statistics

Statistical analysis was done using IBM SPSS Statistics version 24 (IBM, Armonk, NY, USA). The One-way ANOVA was used to analyse the normally distributed data of age and DAS28. Pearson's Chi Square test was used to analyse the relationship between BMD and menopause status. The independent samples Mann–Whitney U-test, Kruskal–Wallis test and Spearman's rho correlation were used to analyse the non-normally distributed data. A p-value of < 0.05 was considered to be statistically significant.

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Ethical Statement

This study was reviewed and approved by the International Medical University, Malaysia Joint Committee on Research and Ethics (IMU-JC), and it has been performed in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki.

Informed Consent

All subjects gave signed informed consent prior to inclusion in the study.

Declaration of Conflict of Interest

All authors have no declaration of conflict of interest.

Results

This was a cross-sectional study of 75 female RA patients and 29 age-matched controls. Table 1 shows the baseline characteristics of the RA patients. There were 20 (26.7%) Malay, 24 (32.0%) Chinese and 31 (41.3%) Indian patients. Five patients (6.7%) were on prednisolone and 51 (68.0%) were on methotrexate. 43/75 (57.3%) of the patients were on calcitriol but all of them had normal corrected calcium values. None of the subjects were on native vitamin D supplements. Table 2 shows the proportion of patients with normal, osteopenia or osteoporosis at each of the DXA measurement sites. Overall, there were 11 (14.7%) patients with osteoporosis, 27 (36.0%) with osteopenia and 37 (49.3%) had normal BMD. Menopause status was significantly associated with BMD at all sites (Mann Whitney U LS p = 0.002, FN p = 0.004, TH p = 0.002). There were significantly more post-menopausal patients in the osteopenia (22/27 [81.5%]) and osteoporosis (10/11 [90.9%]) groups (Pearson's Chi Square p = 0.028). There was no significant correlation between DAS28 and BMD at all sites (data not shown).

Serum OC levels were not significantly different between RA patients compared to healthy controls (p=0.198). There were no significant differences in serum OC levels between the races (Mann-Whitney U p = 0.173) or with menopause status (Mann-Whitney U p = 0.130).

Table 3 shows the correlations between serum OC and age, body mass index (BMI), DAS28, BMD, tender joint count (TJC) and swollen joint count (SJC). Serum OC increased with age (Spearman's rho r=0.230, p=0.047). There was no significant correlation between serum OC and BMI, BMD, DAS28, SJC or TJC. These correlations remained non-significant even after correction for age.

Discussion

Generally, RA patients have been shown to have lower BMD than healthy controls, with a two-fold increase in the presence of osteoporosis.[15] The reason for this systemic osteoporosis is multifactorial. The inflammation present in the joints due to circulating cytokines can lead to increased bone resorption.[2] In addition, glucocorticoids are used to treat RA which can have deleterious effects on BMD. This is apart from the standard risk factors for osteoporosis such as menopausal status. There have only been a handful of studies looking at BMD in non-Caucasian RA patients. In a study of 105 patients with early RA from Vietnam, the prevalence of osteoporosisin in those over the age of 50 was 42.2% at the LS and 41.8% at the FN.[16] A study of 1,322 postmenopausal RA patients from the South Korean KORONA RA registry showed 46.8% with osteoporosis and 44.0% with osteopenia.[17] A study of 304 RA patients from China with a mean age of 50.7 years showed that the prevalence of osteoporosis was 14.2% at the LS, 11.6% at the total hip and 28.0% at the forearm with an overall prevalence of 30.3%.[18] However, the average age of those with osteoporosis was between 60.5 to 63.1 years, depending on site.[18] In a second study of 246 RA patients from South Korea with an age range of 20-79 years, osteoporosis was present in 18.2% at the LS, 7.8% at the total hip with an overall prevalence of 22%.[19] So, from these studies, the numbers of RA patients with osteoporosis increases with age. In our study population with both pre- and postmenopausal patients, osteoporosis was present in 10.7% at the LS

and 9.3% at the FN, which is similar to the studies from China and the second study from South Korea. In the studies from Vietnam and the South Korean KORONA registry, looking at women over 50 or post-menopause, the proportion of patients with osteoporosis increased. Similarly, we found that postmenopausal patients were in the over-whelming majority in the osteopenia (81.5%) and osteoporosis (90.9%) groups. Thus, the proportion of Malaysian RA patients with osteoporosis and osteopenia is comparable to other Asian studies that featured both pre- and postmenopausal patients. Our results are also in keeping with the general finding of an increase in the number of patients affected with osteoporosis with increasing age.

Bone turnover markers can be measured from a blood test and would be a more convenient method to assess BMD compared to DXA. In a recent systematic review, serum OC has been found to be significantly correlated with BMD in postmenopausal but not premenopausal women.[20] However, at an individual level, there is too much inherent variability in the measurement to be able to use it to assess BMD or diagnose osteoporosis in the healthy population.[1]

In Caucasian RA patients, serum OC levels have been found to be higher[5,21], lower[6,22] or no different[7] compared to healthy controls. In the limited number of non-Caucasian studies, serum OC levels were found to be higher in Venezuelan RA patients compared to healthy controls.[23] Japanese postmenopausal RA patients have been shown to have lower serum OC levels compared postmenopausal healthy controls but there was no difference in levels between premenopausal RA patients and their controls.[24] Our study in an Asian RA population contrasts with both those studies in that that there was no difference in serum OC levels between our RA patients and healthy controls and there was no difference in levels between pre- and postmenopausal RA patients. Serum OC levels in our study's RA patients have been shown to significantly increase with age, similar to an Italian study, albeit their subjects were healthy women.[25] In contrast, there was no correlation between serum OC levels and age in Polish RA patients.[4] Thus, from this study, it would seem that measuring serum OC would not differentiate between Malaysian RA patients and healthy controls.

In RA, the cytokines that are produced at sites of inflammation can increase bone turnover and hence accelerate bone loss.[2] Thus, altered bone turnover markers can reflect either BMD changes and/or RA disease activity. However, serum OC levels have be shown not to correlate with BMD in RA patients, both in Europe[3,4] and Japan[26], which is similar to this study. The relationship between serum OC levels and RA disease activity is unclear. This study did not show any correlation between serum OC levels and RA disease activity as measured by the DAS28. This result is similar to 2 recent studies from 2 different centres in Poland, both showing that there was no correlation between serum OC levels and the DAS28.[4,6] Another study from Italy that defined active disease using the presence of swollen and tender joint counts, high inflammatory markers and a poor patient and physician global assessment, showed that serum OC levels were lower in patients with active disease.[9] Other studies done before DAS28 was widely used to assess RA disease activity have looked at correlations between serum OC and inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) with contradictory results; serum OC levels were positively correlated with active disease[8,21] or not related to parameters of disease activity.[10] Even in studies with the same country, there can be inconsistent results. In Japanese RA patients, Suzuki and colleagues found a positive correlation between serum OC and CRP levels[24] but Momohara and colleagues found the opposite, a negative relationship between serum OC levels and ESR/CRP.[26] Thus, as shown from this study and others, it would seem that serum OC levels are not useful in the assessment of RA disease activity.

One of the potential limitations to this study is actually a novel finding. Our study population had 3 different ethnic groups and we showed that there

were no differences in the serum OC levels between the 3 races. OC is encoded by the bone gamma-carboxyglutamic acid-containing protein (BGLAP) gene[27] on chromosome 1.[28] As with any gene, there is a possibility that there are ethnic differences in the gene expression and thus its effect. A study from Sweden showed that the promoter polymorphism rs1800247 of the OC gene was significantly associated with total serum OC but not BMD.[29] A population-based study from Shanghai, China, showed that the same polymorphism rs1800247, was associated with serum OC levels in both men and women, but only with BMD in men.[30] The 298T→C polymorphism of the osteocalcin gene in postmenopausal Japanese women has been shown to be associated with BMD, with the CC genotype subjects having a higher BMD compared to the CT and TT genotypes.[31] In a study of the osteocalcin gene Hind III polymorphism in postmenopausal Korean women, subjects with the hh genotype have higher OC levels.[32] There have been no previous studies in an Indian or Malay population. Furthermore, in the studies that measured serum OC[27,28,30], it was difficult to assess whether serum OC varied with ethnicity as the different studies used different assays, making a direct comparison impossible. We are thus hoping to obtain funding to perform a study on the OC gene polymorphisms and bone health in a larger sample of subjects of different ethnicities in Malaysia. Another possible second limitation is that our study sample size was small, hence less able to detect any significant changes. However, other studies with significant correlations have had similar, or lower numbers of subjects.[5,6,8,23,24]

In conclusion, we have shown that there is no difference in serum OC levels between Malaysian RA patients compared to healthy controls. In RA patients, serum OC levels did not correlate with BMD or RA disease activity. In addition, we found that approximately only 50% of Malaysian RA patients have normal BMD. Not unexpectedly, menopause status remains an important influence on BMD, suggesting that postmenopausal RA patients should be strongly encouraged to have formal assessments of their BMD, especially since the measurement of serum OC levels was not found to be useful in identifying those at risk of low BMD.

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Table 1

Baseline Characteristics of the Rheumatoid Arthritis Patients

	Rheumatoid Arthritis Patients (n=75)	**Healthy Controls** (n=29)
Age (years)*	54.27 ± 6.81	52.62 ± 5.43 a
Serum osteocalcin (ng/mL)**	14.44 (12.99)	11.04 (12.29) b
Disease duration (years)*	8.24 ± 5.28	
DAS28*	4.16 ± 1.20	
ESR (mm/hr)**	38 (38)	
Swollen joint count**	1 (3)	
Tender joint count**	2 (3)	

* Values given as mean ± 1 standard deviation
** Values given as median and interquartile range (IQR)
[a]ANOVA p = 0.247
[b]Mann-Whitney U p = 0.198

Table 2

Bone Mineral Density Status at Different Sites

	Normal (T-score > -1)	**Osteopenia** (-1 < T-score < -2.5)	**Osteoporosis** (T-score >-2.5)
Lumbar Spine	46 (61.3%)	21 (28.0%)	8 (10.7%)
Left Femoral Neck *	43 (57.3%)	24 (32.0%)	7 (9.3%)
Left Total Hip *	52 (69.3%)	21 (28.0%)	1 (1.3%)
Overall	37 (49.3%)	27 (36.0%)	11 (14.7%)

* 1 result missing

Table 3

CorrelationsBetween Serum Osteocalcin and Clinical Features

	Spearman's rho Correlation Co-efficient	**2-tailed Significance (p)**
Age (years)	0.230	0.047
Body mass index (kg/m2)	0.042	0.721
DAS28	-0.057	0.628
Lumbar spine BMD (g/cm2)	-0.198	0.088
Femoral neck BMD (g/cm2)	-0.108	0.359
Total hip BMD (g/cm2)	-0.179	0.127
Swollen joint count	-0.154	0.179
Tender joint count	-0.151	0.357

BMD = bone mineral density