Osteoporosis in Rheumatoid Arthritis: Epidemiology, Pathogenesis and Management

Ka-Wing Lee, Ka-Lai Lee and Man-Choi Wan

Abstract: Rheumatoid arthritis (RA) is a common inflammatory arthropathy of unknown etiology. Its radiological features are well described, which include juxtaarticular osteoporosis and bone erosion in the affected joints. In rheumatology practice, RA and use of oral steroid are the commonest causes for secondary generalized osteoporosis. Over the past decade, there is increasing focus on the relationship between RA and osteoporosis. This is because of the significant morbidity and mortality associated with osteoporotic fractures. The outcome of osteoporosis would certainly be improved if physicians can appreciate and offer appropriate management of this condition in RA patients.

Keywords: Glucocorticoid, morbidity, osteopenia, rheumatoid

Epidemiology and Risk Factors of Osteoporosis in Rheumatoid Arthritis

Cross-sectional studies have demonstrated that there is an increase in fracture rates among Rheumatoid arthritis (RA) patients.1 The odds ratio for morphometric vertebral fracture revealed by spine X-ray in steroid treated postmenopausal RA women was 6.2 when compared to age matched controls from a population based group.2 Another study described the prevalence of radiological vertebral fracture to be 25% and 13%, respectively, among steroid treated and non-steroid treated RA patients.3 About one third of patients with vertebral fracture were symptomatic. On the other hand, when compared to general population, the relative risk for hip fracture in RA was 1.5,4 while a more recent study conducted in Finland noted RA patients carried a three fold increase in risk of hip fracture.5 In a local study, 7% of RA patients were found to have osteoporotic fractures, which were likely to be an underestimation due to the retrospective nature of the study.6

Bone mineral density (BMD) measurement revealed an even higher prevalence of osteopenia (a Z-score of ≤1 SD below the mean value of age- and weight-adjusted control) and osteoporosis (a T-score of ≤2.5 SD below the mean value of young health adults) among RA patients. A 2-fold increase in frequency of osteoporosis was observed in the female patients of Oslo County RA register.7 BMD of the femoral neck and total hip were found to be lower, while no BMD reduction was evident in the lumbar spine. With regard to male RA patients from the same register, there was nearly 2-fold higher in the frequency of reduced BMD (both in spine and hip region) than in a reference population.8 Stafford et al noted in their male RA cohort, the prevalence of osteoporosis over the lumbar spine and hip were 19% and 29% respectively.9

Studies suggested that the loss of BMD in RA patients started in the initial phase of disease. Gough et al studied a cohort of early RA patients who were steroid and DMARD naive.10 BMD was measured yearly and the authors noticed that BMD of patients at presentation did not differ from controls while patients with disease for less than 6 months had significant higher spinal BMD than those with longer duration (>12 months). However, over the first 12 months all patients showed reduction in BMD. Another study which recruited RA patients with disease duration no more than 12 months...
demonstrated that though the overall BMD of spine and hip in early RA patients did not significantly different from normal reference population, there were a significant proportion of patients with reduced BMD (Z-score ≤ -1SD) in one or more body sites, i.e. 45% in women and 51% in men.11

Data from the longitudinal studies suggested continue bone loss did not apply to every RA individual and the degree of BMD changes was variable.12-15 Kroot et al noted in their cohort of RA patients, the reduction of BMD was actually lower than expected from their increased age as compared with age- and sex-matched reference values.12 There was a small but statistically significant increase in mean Z-score. This increase in Z-score could not be explained by the use of hormonal replacement therapy (HRT) or other bone-active agents. This could imply a potential reversibility of bone loss with a control of disease activity. It was noteworthy that the use of bone-active agents (HRT, bisphophonates, or calcitonin) was associated with increase in BMD at all measurement sites while those patients using calcium and vitamin D or not using any osteoporosis treatment were found to have bone loss. Aman et al did not find significant accelerated bone loss within a 2-year follow up period in their community based cohort, for which mainly consisted of patients with mild RA.13

Interestingly, in longitudinal studies, there was more BMD loss at the hip region than at the spine.10 This observation is intriguing since the use of steroid is one of the proposed major factors relating to osteoporosis in RA, which was supposed to affect the lumbar spine more. Possible explanation includes synovitis of the hips, reduced weight bearing due to mobility problem, or an artificial increase in spine BMD secondary to osteoarthritic changes or vertebral collapse.

Epidemiological studies revealed a number of risk factors for bone loss in RA patients (Table 1).2-4,7,10,12,14 Patients' demographic characteristic played an important role, which included increasing age, female gender, menopausal status, low body weight and body mass index. Disease related factors included disease severity or activity, duration, and functional status and mobility of patients. Treatment related factors were the use of steroid and treatment response attained. Moreover, use of methotrexate in high doses and cyclosporin had been implicated for bone loss and osteoporotic fracture. The risk factors identified varied with the method and the characteristics of the cohort studied. Among various studies, multivariate analyses had identified aging, low body weight, impaired functional status or mobility and use of steroid as independent factors predicting the low BMD.4,12

Pathogenesis

It was long believed that the bone erosion in RA was due to the invasion of pannus, while juxtaarticular osteoporosis was related to the presence of large amount of locally produced bone resorbing cytokines. Generalized osteoporosis in RA was previously thought to be contributed by the immobility and the use of steroid or certain DMARDs. However, with recent advances in the pathophysiology of both diseases, there are data suggesting some possible common mechanisms underlying the local and the systemic bone changes. The existence of such common underlying mechanisms were supported by the fact that higher bone loss in the spine and hip has been found in patients with persistently active disease and an association loss of BMD with bone erosion.10,14,15

Components in Bone Metabolism

Osteoblast and osteoclast are the two major types of cell involving in bone remodeling and metabolism. Osteoblast is derived from mesenchymal stem cells in bone marrow and is responsible for production of bone matrix and also play an important role in the calcification process. Osteoclast is a multinucleated cell responsible for bone resorption and is

<table>
<thead>
<tr>
<th>Table 1. Risk factors for osteoporosis in RA patients</th>
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<tr>
<td><strong>Demographic</strong></td>
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<tr>
<td>increasing age</td>
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<tr>
<td>female</td>
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<tr>
<td>lower body weight/bone mass index</td>
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<tr>
<td><strong>Disease-related</strong></td>
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<tr>
<td>longer disease duration</td>
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<tr>
<td>increasing disease severity</td>
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<tr>
<td>disease impact on functional status and mobility</td>
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<tr>
<td><strong>Treatment-related</strong></td>
</tr>
<tr>
<td>steroid</td>
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<tr>
<td>high dose methotrexate (100-1000 mg/m²)</td>
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<tr>
<td>cyclosporine A</td>
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<tr>
<td>treatment response</td>
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formed from phagocytic precursors of the monocyte-macrophage lineage. The osteoclast precursors express the receptor activator for nuclear factor κB (RANK) and differentiate into functional osteoclast in the presence of macrophage-colony stimulating factor (M-CSF) and RANK ligand (RANKL). RANKL, also known as osteoprotegerin ligand (OPGL), is found in osteoblast. Osteoprotegerin (OPG), a soluble non-signaling receptor of RANKL, would inhibit the binding of RANKL to RANK on osteoclast and its precursor (Figure 1). Further details can be found in a number of comprehensive reviews on the OPG/OPGL/RANK signaling pathway.16,17

Pathological Changes in Bone Metabolism: Implication for Bone Erosion and Osteoporosis

Under normal circumstances, activities between osteoblast and osteoclast are well-coordinated. In generalized osteoporosis, there is an uncoupling of the bone remodeling process resulting in a relative excess in bone resorption by osteoclast as compared to bone formation by osteoblast. On the other hand, osteoclast is also noted to play an important role in focal erosion of RA joint, as osteoclast has been identified at the sites of bone erosion.

Osteoclast precursor, which belongs to CD14+ monocyte/macrophage lineage, has been found in the synovial tissue of RA subjects.18 Differentiation of these osteoclast precursors is promoted by the RANKL produced by activated synovial fibroblast and T lymphocytes found in RA synovial tissue.19-21

Apart from activated cells found in rheumatoid synovial tissue that could participate in the bone remodeling, cytokines and local factors which are produced during the inflammatory process are also known to have the ability to affect the balance of bone metabolism. Key player cytokines, like TNFα and IL-1, are thought to be capable to act either directly or indirectly (via increase of RANKL expression in osteoblast) on osteoclast. Activated osteoclast, together with metalloproteinases from synovial fibroblast and monocytic phagocytes, would in turn responsible for the tissue destruction found in rheumatoid joints.

With regard to generalized osteoporosis in RA, there is postulation about the increased level of TNFα, IL-1 and IL-6 could be principal humoral factors mediating the process. Hirayama et al noted an increase in the extent of lacunar resorption carried out by osteoclasts formed from the
circulating precursors in RA patients as compared to control.\(^{22}\) They suggested that it was the increased in osteoclast functional activity rather than osteoclast formation playing a major role of generalized bone loss in RA. Though, in that particular study, they were unable to demonstrate any significant augmentation of osteoclast formation or lacunar resorption when TNF\(\alpha\), IL-1 and IL-6 were added to their cell cultures from peripheral blood mononuclear cell; it was still possible that these cytokines would act on non-circulating osteoclast precursors or indirectly via the osteoblast lineage.

**Effect of Steroid on Bone Metabolism** (Table 2)
There are a number of pathogenic mechanisms underlying bone loss and negative calcium balance in the use of steroid.\(^{23,24}\) Steroid exerts effects on osteoblast formation and increases the apoptosis of osteoblast and osteocyte. Osteoclastogenesis is transiently increased, which is then decreased subsequently. Excessive steroid would also antagonize gonadal function. Reduced calcium intestinal absorption and increase in renal excretion lead to a negative calcium balance. Of the above mechanisms, detrimental effects of steroid on osteoblast and bone formation are the major mechanism. However, steroids also inhibit the synthesis of TNF\(\alpha\) and IL-1, which might be an advantage when used to control inflammatory activity.

**Effect of Methotrexate (MTX) on Bone Metabolism**
Osteoporosis and fracture has been reported in children using large doses of MTX (100-1000 mg/m\(^2\)) for leukaemia and long-term low-dose MTX in RA and psoriasis. In animal study, high dose MTX has been showed to inhibit osteoblast function.\(^{25}\) This raises concern about further bone loss in RA patients who are already prone to osteoporosis. Recent case-control and follow up studies suggested that there was no adverse effect of low-dose MTX (mean dose at 10 mg/wk) on bone density.\(^{26,27}\) In an in vitro study, Minaur et al found that MTX did not appear to exert a direct inhibitory influence on the proliferation and differentiation of cells of the osteoblast lineage.\(^{28}\) Overall, the update data are reasonably reassuring for clinician using long-term low dose MTX.

**Management of Osteoporosis in RA**
It is obvious that osteoporosis in rheumatoid arthritis is a significant problem in RA patients. However, there is no specific guideline available for clinician to manage this particular clinical problem, apart from general guideline management of osteoporosis and on steroid-induced osteoporosis.\(^{29,30}\) Even a clinical guideline is available, there are evidence showing that major gaps do exist between recommendations and daily practice.\(^{31,32}\)

**Diagnosis, Case Identification and Screening**
The use of dual-energy X-ray absorptiometry (DEXA) is the gold standard for the diagnosis and monitoring of patients with osteoporosis. Investigators are trying to find other diagnostic techniques, which are cheaper, more portable and convenient to use. Quantitative ultrasound (QUS) is one of the techniques being studied, because it has been shown to be able to discriminate between normal and osteoporotic postmenopausal women, independent of BMD. However, Sambrook et al could not found any additional discriminatory power in QUS over conventional DEXA measurement.\(^{33}\)

Effort has also been devoted to develop clinical screening tools to identify RA patients who are at high risk of osteoporosis.\(^{34-37}\) In such a large population, this is particularly relevant from the cost-effectiveness perspective. Lems proposed to perform BMD measurement in RA patients if they had two or more of the 3 criteria; namely, high disease activity (CRP >20 mg/L or ESR >20 mm/hour), older age (women >50 or men >60) and immobility (Steinbrocker score \(\geq\) 3 or HAQ score \(\geq\) 1.25).\(^{34}\) This proposed criterion was tested in a group of Spanish patients. Their sensitivity for the diagnosis of osteoporosis was 86% while the specificity was 43%.\(^{35}\) On the contrary, Kvien et al, argued that clinical markers are weak markers as compared to increasing age and low body mass index (BMI).\(^{36}\) They further modified the initial criteria suggested by Lems by inclusion of weight and the ever use of corticosteroid as additional items (three

**Table 2. Mechanisms for Steroid-induced Osteoporosis**

<table>
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<tr>
<th>1. Osteoblast</th>
<th>↓ osteoblastogenesis, ↑ apoptosis of osteoblast and osteocyte</th>
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<tr>
<td>2. Osteoclast</td>
<td>↑ osteoclastogenesis (early stage), ↑ functional activity</td>
</tr>
<tr>
<td>3. Parathyroid hormone</td>
<td>↑ PTH synthesis and secretion, ↑ PTH-sensitivity</td>
</tr>
<tr>
<td>4. Sex hormone</td>
<td>↓ synthesis and secretion of sex hormone</td>
</tr>
<tr>
<td>5. Calcium balance</td>
<td>↓ intestinal Ca(^{2+}) absorption, ↑ renal Ca(^{2+})=xcretion</td>
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out of five items to be fulfilled) and tested on the cohort of patients in the Oslo Rheumatoid Arthritis Register. They were able to achieve a sensitivity of 74% and 67% in women and men respectively, while the specificity were 57% and 50%.

Though specific guideline for screening of osteoporosis in RA patients is lacking, it should be noted that there are recommendations for screening in various setting for which RA patients may fit into. For RA patients who are receiving or to be started on long-term steroid therapy, should have a BMD measurement according to the ACR recommendations for prevention and treatment of steroid-induced osteoporosis.

An annual follow up BMD examination probably would be sufficient for patients receiving therapy to observe for bone loss. In postmenopausal women, US Preventive Services Task Force recommends for those 65 years of age or older should be screened routinely for osteoporosis. They also suggest lowering the screening to 60 years of age for women at increased risk for osteoporotic fracture. In a local clinical management guideline developed by a panel of experts from various specialties, a case finding approach is recommended for identifying subjects with clinical risk factors, medical conditions associated with osteoporosis, an X-ray report of osteopenia, and the occurrence of low-trauma fracture. Putting these recommendations together, RA patients should be screened for osteoporosis if they meet the criteria in Table 3.

### Non-pharmacological Management

Adequate dietary calcium intake and ample sunlight exposure should be emphasized. Patients should also be advised to stop cigarette smoking and moderating their intake of alcohol. Exercise is another important issue to be discussed. Weight bearing exercise would have a positive effect on bone health, and should be encouraged. However, attention should be paid to those with active joint inflammation for whom the way and the degree of exercise should be tailored according to joint involved and severity of inflammation. Physiotherapist opinion would be most helpful. Moreover, balancing exercise including Tai Chi have been found to decrease the risk of fall and would be beneficial for RA patients with osteoporosis.

### Control of Disease Activity

A study of a cohort of active RA patients starting on a new DMARD demonstrated prevention of bone loss at the lumbar spine and hip over a 2 year period despite the absence of specific osteoporosis therapy. The authors also found that there was an inverse relationship between the change in disease activity score (DAS) over the 0-3 months and the percent change in spine over 1 year. In a recent report, bone loss in hand correlated with radiological progression as measured by Larsen score, for which were both strongly predicted by therapeutic response at 6 months. Therefore, it is evident that control of rheumatoid process is important in the prevention of osteoporosis in RA patients.

### Minimize the Use of Steroid

Apart from being an adjuvant therapy, systemic steroid is indicated in the treatment of aggressive extra-articular manifestations of RA like rheumatoid vasculitis and lung disease. However, when the disease is under better control, the dosage of steroid should be tapered down. It is well known that BMD would improve and the fracture risk would decrease after discontinuation of steroid. On the other hand, in the study conducted by Italian Study Group, the risk of vertebral fracture was increased by 70% for a one unit increase in HAQ, but only by 3% for an extra gram of cumulative prednisolone. Therefore, it was suggested that in some circumstances, the adverse effect of steroids on bone might be outweighed by improved disease control leading to less disease related bone loss.

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**Table 3. Screening for osteoporosis in RA patients – a reminder**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Condition</th>
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<tr>
<td>All postmenopausal women &gt;65</td>
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<tr>
<td>Steroid use</td>
<td>initiating long-term steroid (&gt;6 months) long-term user at a dose ≥7.5 mg/d</td>
</tr>
<tr>
<td>Existence of prevalent fragility fracture (vertebral or non-vertebral)</td>
<td></td>
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<tr>
<td>X-ray revealing significant osteopenia</td>
<td></td>
</tr>
<tr>
<td>Other factors to be considered</td>
<td>Low body weight Family history of osteoporosis or fragility fracture Functional dependent &amp; lack of outdoor activity Active and uncontrolled arthritis</td>
</tr>
</tbody>
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Vitamin D and Calcium Supplement

In general, universal prescription of vitamin D is not recommended in Hong Kong, as there is sufficient sunlight exposure. However, it would be sensible to prescribe 400-800 U to RA patients who are institutionalized or lack of outdoor activities. Calcium supplement would be needed if the dietary calcium intake is insufficient. However, it should be aware that calcium alone would not be adequate to treat osteoporosis or prevent steroid induced osteoporosis. The combination of vitamin D and calcium would be insufficient in the primary prevention of steroid induced osteoporosis, though in some secondary prevention studies reveal a modest effect on spine BMD but not at the femoral neck.

Hormonal Replacement Therapy

Steroid use is associated with hypogonadism in some of the subjects and is one of the mechanisms leading to the loss of bone mass as mentioned above. Therefore, estrogen replacement for women and testosterone for men are suggested if hypogonadal state is documented, unless there are contraindications. However, it should be noted that there is no good evidence of hormonal replacement for primary prevention against bone loss in steroid induced osteoporosis.

Bisphosphonates

In the past few years, bisphosphonates have become one of the most popular therapeutic agents used in the treatment of osteoporosis. It probably is also a very useful agent in the treatment of RA patients suffering from osteoporosis. Both alendronate and risedronate have been shown to be effective in the treatment and prevention of fragility fracture in postmenopausal women, and its efficacy in men has also been documented. The effect of alendronate is more sustained than estrogen therapy after discontinuation of treatment. In steroid user, both alendronate and risedronate have been shown to increase the BMD of spine and hip together with significant reduction of number of vertebral fracture. Many of the subjects in these studies were RA patients. Though there is a suggestion to stop the bisphosphonate treatment after a 2 to 3 years course, it has been shown that alendronate should be continued in patients who were continued on steroid at dose equivalent to >6 mg prednisolone.

Several placebo-controlled trials have shown etidronate is effective in maintaining and increasing the BMD of the lumbar spine. Adachi et al, found that intermittent etidronate could result in fewer vertebral fractures in steroid user. However, they noted that there was no difference in the femoral neck BMD between groups.

There are discussions about the additional effect of bisphosphonates in suppression of inflammatory activity and prevention of local bone loss in inflammatory arthritis. Non-nitrogen containing bisphosphonates (clodronate and etidronate) appear to exert some of their effects on the macrophage and osteoclast cell lines. However, there are conflicting results from clinical interventional trials with regard to whether etidronate has effect on radiological progression in RA patients. On the other hand, nitrogen-containing bisphosphonates such as pamidronate and alendronate are also noted to have effects on the inflammatory processes. They have been shown to suppress in vitro cell proliferation, cell growth, cell migration, costimulatory activity for T cells, antigen presenting cell function and inhibition of stimulated secretion of proinflammatory cytokines IL-1β and TNFα. Obviously, further studies are necessary with regard to the action and effect of bisphosphonates in inflammatory arthropathies.

Use of Other Bone-active Agents

Calcitonin could also be used in the treatment of osteoporosis, however, its efficacy is less consistent compared to bisphosphonates. Selective estrogen receptor modulator (SERM) is now available for the treatment of postmenopausal osteoporosis. Nevertheless, very limited data is available on its use in steroid-induced osteoporosis or in inflammatory arthritis. Bone forming agent would be an interesting agent to explore because of its capability in increasing the BMD to a larger extent than the anti-resorptive agents.

Conclusion

It is now obvious that there is a close relationship between RA and osteoporosis, be it local or generalized osteoporosis. As rheumatologists and physicians looking after patients suffering from RA, it would be important for us to be aware of the scope of the problem. Appropriate screening and treatment should be initiated when indicated. Moreover, one should manage osteoporosis early before a significant loss of BMD. One should not miss the opportunity in preventing further problem in RA patients who are already affected by a
chronic debilitating disease; otherwise it would result in additional morbidity and mortality secondary to the complications of osteoporotic fractures.

References

RA AND OSTEOPOROSIS


