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Osteoporosis in Rheumatoid Arthritis

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Involvement of the bones in rheumatoid arthritis (RA) has been recognized for many years. Patients with RA develop both periarticular or juxta-articular and generalized osteoporosis and have an increased risk of fracture. Periarticular osteoporosis appears to be predominantly mediated by local mechanisms associated with rheumatoid synovitis and is one of the earliest radiological signs of RA. Generalized osteoporosis is also common in RA and its etiology is considered to be multifactorial.

Periarticular Osteoporosis

Development of osteopenia in the vicinity of inflamed joints is a common clinical feature of RA. This local osteopenia occurs early in the course of the disease, and is evident in some patients only a few months after the onset of symptoms, when erosive changes of the bone or thickening of the synovium are not yet evident [1,2]. The diagnosis of periarticular osteoporosis has traditionally been made using plain radiographs of the peripheral joints. However, this method is imprecise and inadequate for the quantification of periarticular bone loss. Recent advances in non-invasive radiological techniques such as dual-energy X-ray absorptiometry (DXA) have allowed the direct measurement of bone mass.

We have attempted to quantify bone mass near inflamed joints using DXA. The bone mineral density (BMD) of the proximal phalanx was measured by a DXA apparatus (Lunar DPX-L) using the program for small animal appendicular scanning. The region of interest (ROI) was positioned at five different sites; ultradistal, distal, midportion, proximal and ultraproximal. Phalangeal BMD was measured in 10 patients with early RA and 10 patients with chronic RA, and was compared with normal values obtained in age-matched female controls (Fig. 1). The BMD at the midportion of the proximal phalanx was similar in controls and patients with early RA, whereas the BMD of the periarticular regions (ultradistal and ultraproximal regions) was decreased in the patients with early RA. In contrast,

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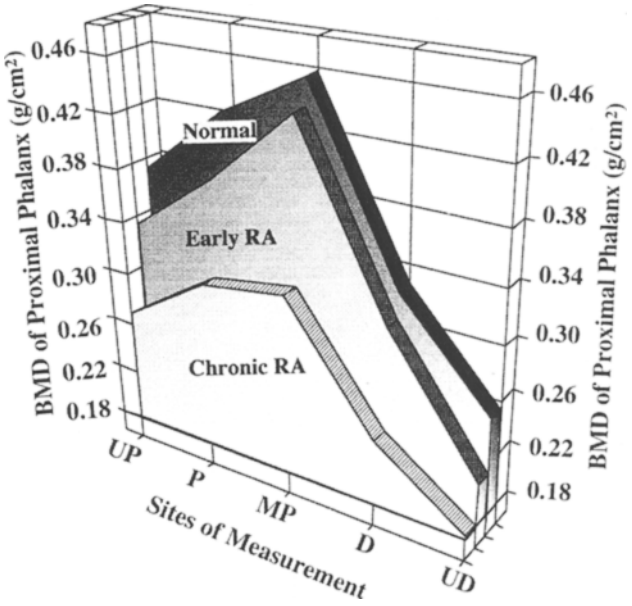

Fig. 1. Bone mineral density (BMD) of the proximal phalanx, determined at five different sites by DXA in normal controls, patients with early rheumatoid arthritis (RA) and patients with chronic RA. UP, ultraproximal; P, proximal; MP, midportion; D, distal; UD, ultradistal.

patients with chronic RA showed bone loss at all sites. This study confirmed that localized bone loss occurs at the regions near the inflamed joints in early RA but appendicular bone loss at sites distant from the inflamed joints does not occur in the early stage of this disease. However, diffuse osteopenia of the appendicular bones occurs in the chronic stage of the disease process.

Pathogenesis

The pathogenesis of rheumatoid periarticular osteopenia is still not fully understood. Sambrook et al. [2] reported that the decrease in radial BMD in patients with early RA was significantly more rapid at the periarticular site compared with normal healthy controls whereas the rate of decline of lumbar BMD was similar in RA patients

and controls. The decrease in periarticular BMD was correlated with parameters of rheumatoid activity, such as the serum C-reactive protein level or articular indices. These observations suggest that rheumatoid periarticular osteopenia is closely associated with synovial inflammation.

The following factors have been implicated in the development of periarticular osteopenia: immobilization of the affected joints by pain and deformity, as well as local release of factors such as inflammatory cytokines and prostaglandins from adjacent sites of synovial inflammation [3,4]. Previous histological studies of bone specimens obtained from patients with chronic RA have demonstrated an increase in both bone resorption and bone formation, suggesting increased bone turnover [5]. However, periarticular osteopenia develops in early RA when erosive changes of the bones or thickening of the synovium are not yet evident.

The acceleration of bone resorption has been suggested to be caused by inflammatory cytokines or chemical mediators released from inflamed joints into the adjacent bones. Osteoclasts are derived from multilineage hematopoietic stem cells. Several local factors may have a role in the regulation of osteoclast maturation and activation, including cytokines (interleukin-1 (IL-1), IL-6 and tumor necrosis factor), prostaglandins, and colony stimulating factors [6,7]. Since rheumatoid synovium produces these cytokines and prostaglandins [8–10], diffusion of such factors into the adjacent bone might stimulate bone resorption.

Our previous study demonstrated that a rat model of adjuvant-induced arthritis showed localized bone loss with a distribution similar to that in human RA [11]. Bone marrow from rats with adjuvant-induced arthritis formed a significantly larger number of osteoclast-like cells, suggesting that the number of osteoclast precursors was increased in the marrow. Furthermore, formation of osteoclast-like cells and resorption lacunae on ivory slices was markedly stimulated by the addition of marrow supernatants from rats with adjuvant-induced arthritis to bone marrow cultures from both control and arthritis rats. These findings suggest an increase in osteoclast-inducing factors in the bone marrow of arthritis rats. The inhibition of marrow supernatant-stimulated osteoclast formation by specific antibodies against inflammatory cytokines indicated that one of the factors present in arthritis bone marrow was IL-1 [11]. In addition to increased resorptive activity, colony formation by osteogenic precursor cells was decreased in bone marrow cultures obtained from sites adjacent to inflamed joints and the serum osteocalcin level was also decreased [11]. Previous studies have demonstrated that systemic administration of IL-1 induced a decrease in serum osteocalin and suppression of osteogenic precursor cell colony formation in marrow cultures [11,12]. Thus, a local increase in IL-1 could induce suppression of bone formation. On the basis of these findings, loss of the balance between bone resorption and formation, possibly mediated through an increase in IL-1 in the bone marrow, may contribute to the development of periarticular osteopenia in inflammatory arthritis.

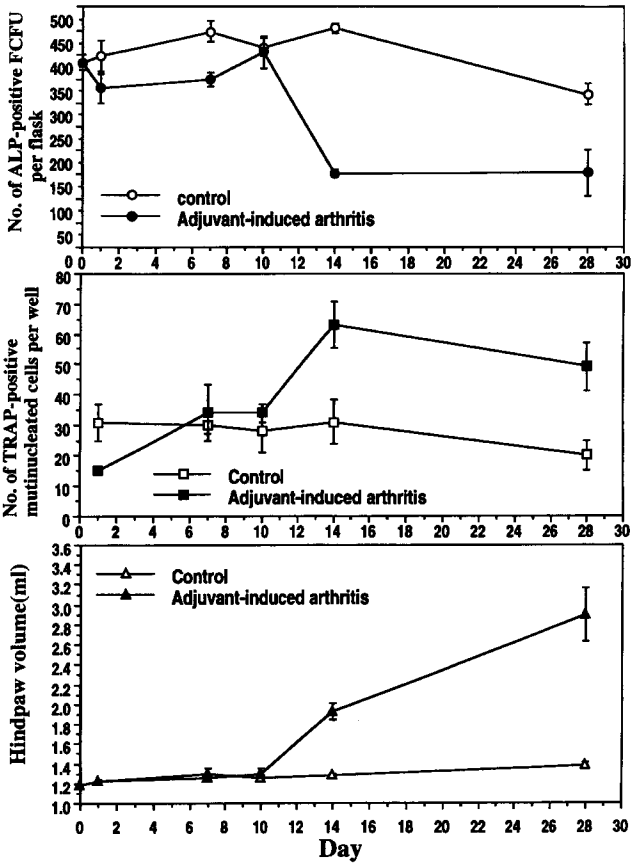

Fig. 2. Serial changes of hindpaw volume and the number of osteogenic precursor cell colonies (ALP-positive FCFU) and osteoclast-like (TRAP-positive) cells in bone marrow culture in rats with adjuvant-induced arthritis.

To clarify the time course of changes of osteogenic and resorptive potential during the development of polyarthritis, we investigated the formation of osteogenic precursor cell colonies and osteoclast-like cells in bone cultures obtained from adjuvant-inoculated rats on days 1, 7, 10, 14 and 28. As shown in Fig. 2, polyarthritis developed 10–11 days after bacterial inoculation. At the same time as the onset of arthritis (on day 14), the formation of osteogenic precursor cell colonies was decreased and supression of the osteogenic potential of the bone marrow persisted until day 28. Similarly, the formation of osteoclast-like cells in bone marrow cultures was significantly increased on day 14 when polyarthritis developed. These results suggest that the suppression of osteogenic potential and the acceleration of bone resorptive potential occur in the bone marrow at the same time as polyarthritis develops.

Generalized Osteoporosis

Generalized osteoporosis is well documented in RA. Generalized axial and appendicular bone loss at sites

distant from inflamed joints has been demonstrated by radiographs, computed tomography (CT), and DXA [13,15]. In addition, bone histomorphometric studies have confirmed a high frequency of osteoporosis in patients with RA [16]. The clinically important endpoint of osteoporosis is fracture and an increased frequency of vertebral and hip fractures has been reported in RA patients [17,18]. However, the relative importance of the contribution from the disease itself and that from confounding factors such as immobility and corticosteroid therapy is not fully understood.

Bone Turnover State

Bone turnover has been investigated in RA patients but the data obtained have been conflicting, probably due to differences in the patient populations investigated. There is much information available regarding the markers of bone turnover status. The levels of calcium-regulating hormones, such as parathyroid hormone, calcitonin and 1,25-dihydroxyvitamin D_3 in RA patients have been reported to be similar to those in healthy controls [19]. Most studies have demonstrated decreased levels of serum osteocalcin, a marker of osteoblastic activity, in RA patients [20,21]. Decreased bone formation was also confirmed by histomorphometric studies of iliac crest biopsy specimens from non-steroid-treated RA patients [22]. In that study, the mean wall thickness, an indicator of bone formed per remodelling unit, was significantly reduced in RA patients, whereas mean interstitial bone thickness or osteoid surface was unchanged. These results suggest that reduced bone formation is the predominant mechanism of bone loss in RA.

On the other hand, a study by Gough et al. [23] demonstrated increased excretion of pyridinium cross-links in early RA. They reported that the excretion of pyridinoline and deoxypyridinoline was significantly increased in RA patients who received no corticosteroids or disease-modifying drugs compared with controls, and that pyridinoline excretion was associated with increased RA activity and BMD loss at the femoral neck. Thus, increased bone resorption may also be an important factor in the generalized bone loss of patients with active RA.

Pathogenesis

The mechanism of generalized osteoporosis in RA is multifactorial and the following factors have been proposed: systemic effect of rheumatoid inflammation, immobility, drugs such as corticosteroids, endocrine changes associated with menopause, nutritional problems, and weight loss. Important factors contributing to the development of generalized osteoporosis might differ between axial bones such as the spine neck and sites distant from the inflamed joints of appendicular bones.

1. *Rheumatoid Activity and Immobility.* There are several reports suggesting that the axial BMD may be affected by disease-dependent mechanisms. Laan et al. [24] reported that disease activity independently contributed to axial bone loss, especially in the proximal femur. A study by Gough et al. [24] showed that patients with RA had generalized skeletal bone loss early in the disease and that this bone loss was associated with rheumatoid activity [28]. Since increased serum levels of IL-1 and IL-6 have been reported in RA patients, an excess of these inflammatory cytokines could cause suppression of bone formation and acceleration of bone resorption. However, it is difficult to clarify the relative importance of the contribution of impaired mobility associated with active RA and factors related to the inflammatory process itself.

In addition to the direct influence of disease activity, immobility has been suggested to be an important determinant of bone loss in RA. Many studies have demonstrated a close association between functional capacity and axial BMD [14,24,26]. According to previous studies, the influence of functional impairment is greater on femoral BMD than on spinal BMD.

2. *Treatment*

Corticosteroids. Corticosteroids have a well-documented deleterious effect on bone turnover [27]. An excess of corticosteroids produces bone loss by suppressing osteoblastic activity and increasing osteoclastic bone resorption. Although the suppression of osteoblasts in apparently a direct effect of corticosteroids, the increased bone resorption is caused by secondary hyperparathyroidism as a result of decreased intestinal calcium absorption and increased renal excretion of calcium [28]. Evidence suggests that corticosteroid-induced bone loss is dose-dependent. However, it is still controversial whether low-dose corticosteroids cause significant bone loss in RA patients. A recent study showed that corticosteroid therapy prevented the progression of bone destruction in RA [29]. Thus, the beneficial effect of corticosteroids in controlling the inflammatory process might overcome the deleterious effect on bone metabolism. Although several studies have suggested that low-dose corticosteroid therapy for RA is not harmful to the skeleton [30], most previous studies have shown a trend toward lower bone mass and an increased risk of fractures in RA patients on corticosteroid therapy [26,31,32]. Michel et al. [32] reported that use of corticosteroids in women is an important risk factor for fractures and that the 5-year probability of fracture was 34% in female patients on 5 mg/day or more of prednisone.

We analyzed the BMD of the lumbar spine and radius in 39 corticosteroid-treated and 35 non-corticosteroid-treated patients with RA who had a similar level of disease activity. As shown in Fig. 3, a significant decrease in lumbar BMD and a trend toward a lower BMD of the distal one-third of the radius were observed in patients taking corticosteroids. This suggests that the influence of corticosteroids on bone mass is more

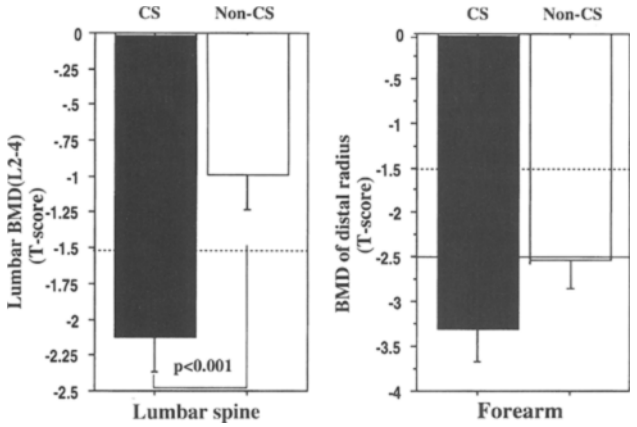

Fig. 3. BMD of the lumbar spine and the distal one-third of the radius in RA patients with or without corticosteroid therapy. CS, corticosteroid-treated patients; non-CS, non-corticosteroid-treated patients.

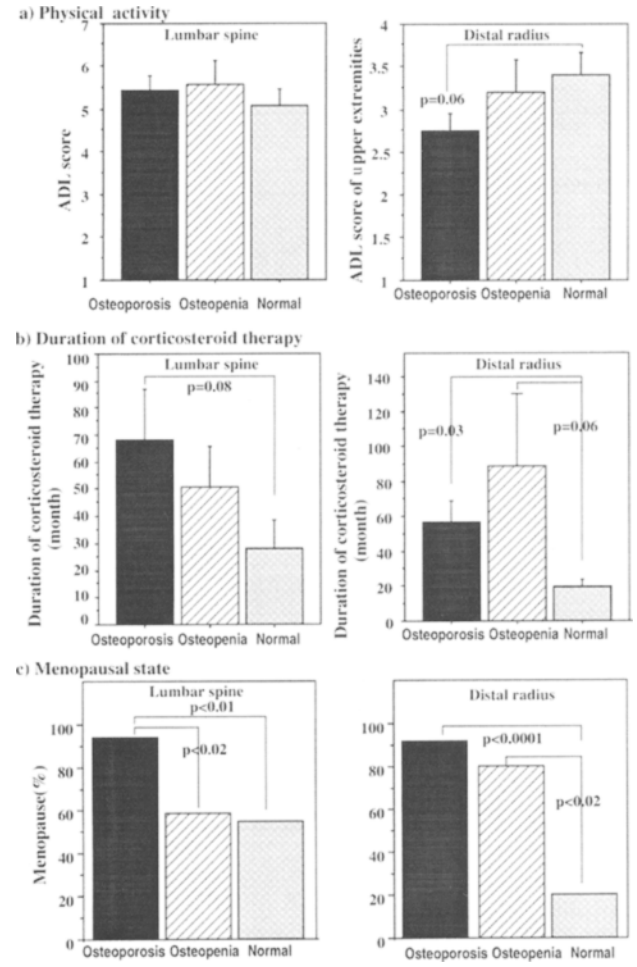

Fig. 4. Effect of physical activity (ADL, activities of daily living), duration of corticosteroid therapy and menopausal status on the BMD of lumbar spine and the distal one-third of the radius.

prominent in the axial bones. To identify the risk factors for corticosteroid-induced bone loss in RA, corticosteroid-treated patients were divided into three groups based on the extent of bone loss: (1) osteoporosis (*T*-score (deviation from young adult mean) > -2.5), (2) osteopenia (*T*-score -2.5 to -1.5), and (3) normal (*T*-score > -1.5). Factors influencing bone loss were compared between groups. Decreased physical activity was a risk factor for appendicular bone loss, although there was no correlation between physical activity and lumbar BMD. Menopausal status and a long duration of corticosteroid therapy were risk factors for both axial and appendicular bone loss (Fig. 4). Accordingly, corticosteroid therapy should be carefully considered for patients who have risk factors such as a postmenopausal status and reduced physical activity.

Methotrexate. Methotrexate is a folate antagonist that has recently been used widely in the treatment of RA. Methotrexate osteopathy, characterized by bone pain, osteoporosis and fractures, has been reported in association with high-dose therapy for malignancy [33,34]. In addition, a recent study demonstrated that prolonged low-dose methotrexate therapy causes osteopenia in animals by increasing bone resorption and decreasing bone formation [38]. These findings suggest that methotrexate might exacerbate osteopenia associated with RA. In an animal model of inflamatory arthritis, however, low-dose methotrexate exhibited a favorable effect on abnormal bone metabolism and bone loss [36]. Despite this, it is possible that low-dose methotrexate might promote osteopenia in patients who already have multiple risk factors, such as postmenopausal status or a young age (children), impaired physical activity, and corticosteroid therapy, since 2 cases of methotrexate osteopathy have been reported in postmenopausal patients with rheumatic disease [37].

Other Contributing Factors (Sex, Menopause and Nutrition)

There have been no uniform data regarding the effect of sex differences on the BMD of RA patients. However, male RA patients on corticosteroid therapy have a lower risk of fracture compared with female patients taking corticosteroids [32]. In addition, changes in estrogen levels complicate our understanding of the pathogenesis of oosteoporosis associated with RA, since perimenopausal or postmenopausal women are mainly affected by this disease. Previous reports have suggested that the influence of corticosteroids on serum osteocalcin and axial bone mass is more evident in postmenopausal patients. In addition to the changes of estrogen, a reduced DHEAS level (which might increase the risk of osteoporosis) has been reported in non-corticosteroid-treated postmenopausal women with RA [38].

Calcium deficiency due to decreased intestinal calcium absorption [39] and weight loss were also reported as factors contributing to axial bone loss [26,40].

Summary

Periarticular osteopenia of appendicular bones occurs early in the course of RA. Loss of the balance between bone resorption and formation contributes to the development of perarticular osteopenia and might be mediated through increased production of cytokines and prostaglandins by the synovium and bone marrow. Generalized osteopenia is also common and leads to an increased risk of fracture. Although the pathogenesis of this osteopenia is considered to be multifactorial, disease activity, immobility, corticosteroids and menopausal status are the important determinants.

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