Bone loss of the radius in rheumatoid arthritis

Comparison between 34 patients and 40 controls

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We measured bone mineral density (BMD) in the radius by dual energy X-ray absorptiometry in 34 patients with rheumatoid arthritis (RA) and in 40 healthy controls. The BMD in RA patients in their fifties and sixties, but not in their forties and seventies, was significantly lower than that in the control subjects. The decrease in total radial BMD correlated with grip strength, RA activity and RA stage. The decrease in distal radial BMD correlated with RA activity, but not with grip strength. The levels of serum parathyroid hormone, alkaline phosphatase, and urinary hydroxyproline/creatinine were significantly higher in the patients. From these findings, we suggest that the bone loss in RA patients is affected by severity of inflammation, disuse, postmenopausal osteoporosis and secondary hyperparathyroidism.

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Bone loss in patients with rheumatoid arthritis (RA) may be caused by various factors, such as cytokines produced by the inflammatory synovium, local and systemic disuse, administration of corticosteroids, and secondary hyperparathyroidism followed by inadequate incorporation of calcium (Kennedy et al. 1975, Reid et al. 1982, Sambrook et al. 1987, Joffe and Solomon 1991). The severity of the bone loss may vary from region to region, since the causative factors and their strength are not consistent among all patients. We scanned the distal para-articular portion of the radius, which is mainly composed of cancellous bone, and the proximal mid-portion, mainly composed of cortical bone in RA patients (Schlenker et al. 1976). We also analyzed the relationship between the bone loss in each portion of the radius and different causative factors.

Patients and methods

34 consecutive women with rheumatoid arthritis were involved in this study. All patients fulfilled the diagnostic criteria of the American Rheumatism Association (Arnett et al. 1987). The mean age of the patients was 61 (40–79) years and the average duration of the disease was 12 (0.5–34) years. The RA stage as defined by Steinbrocker et al. (1949) was I in 5 patients, II in 6, III in 8, and IV in 15. 40 female volunteers without any systemic diseases also participated in the study as control subjects; their average age was 58 (40–79) years. 29 women were postmenopusal among the RA patients and 27 among the controls.

Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DEXA) (model XR-26, Norland Co.). Bone scanning was carried out from the mid-portion of the right forearm to the wrist by using General Scan Mode. 3 regions of interest were created, including the full width of the radius with 1 cm length in the distal two-, three-, and four-tenths of the whole length of the radius, which was measured previously by plane radiograms. BMD in each region (rBMD) was then measured with accessory software. BMD was normalized for the difference in age, by calculating the ratios of rBMD values in RA patients to the average value of the control subjects in the same decade (nBMD). To evaluate the difference between bone loss in the distal portion and that in the proximal portion, ratios of nBMD in the distal two-tenths region to that in the distal four-tenths (0.2/0.4 nBMD) were also calculated—i.e., the smaller the 0.2/0.4 nBMD, the severer would be the bone loss in the distal portion. To determine factors which might affect the bone loss, grip strength in the right hand and serum and urinary chemical bone markers (serum parathyroid hormone [PTH], alkaline phosphatase [ALP], osteocalcin [BGP], and urinary hydroxyproline/creatinine [Hyp/Cr]) were measured in all patients and controls. To distinguish the factor of inflammation and that of disuse, the Lansbury in-

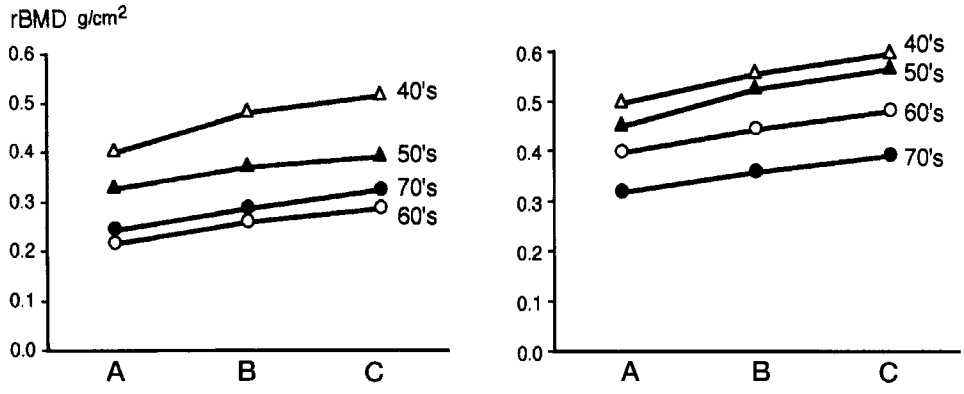

Figure 1. Difference in rBMD among regions—distal 2/10 (A), 3/10 (B), and 4/10 (C) of radius—in each decade in RA patients (left) and control subjects (right).

dex (Lansbury 1966), without counting the grip strength (AI), was calculated in all patients. The AI was considered to be the indicator of disease activity—i.e., the severity of inflammation. From the data obtained, relationships between these factors and the following parameters of the BMD were determined: (1) rBMD, (2) nBMD, (3) the total nBMD in three regions (total nBMD), (4) 0.2/0.4 nBMD.

Statistical analysis was done by using the Student's t-test and Pearson's correlation coefficient. P-value less than 0.05 was considered significant.

Results

1. BMD and age

The rBMD in the control subjects declined linearly with age and that in the distal two-tenths region was always lower than that in the distal four-tenths. The RA patients in each decade had a lower rBMD in each region than the control subjects did (Figure 1). The total nBMD in the RA patients in their fifties and sixties, but not in their forties and seventies, was lower than that in control subjects in the same decade (Figure 2). The 0.2/0.4 nBMD in the RA patients did not differ significantly with the decade.

2. BMD and grip strength

The total nBMD in the RA patients correlated positively with the grip strength (r 0.49, p 0.003). No significant difference was observed in the degree of nBMD reduction, accompanied by the decrease in grip strength among regions, as there was no correlation between 0.2/0.4 nBMD and grip strength (r 0.26, p 0.1).

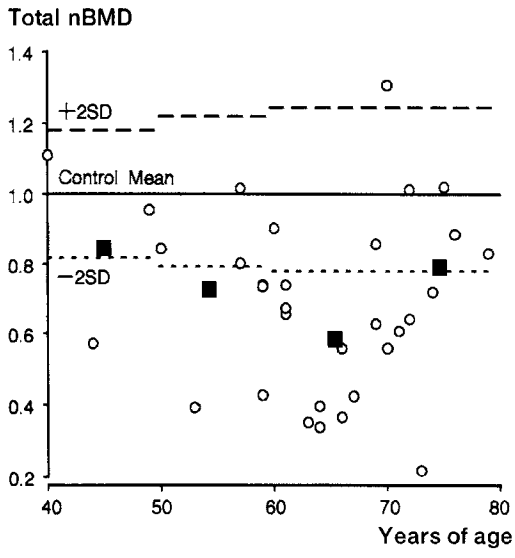

Figure 2. Relationship between total nBMD and age in RA patients (○). P-values for RA means (■) compared with controls were 0.09, 0.003, 0.0001 and 0.07 for age groups 40's, 50,s, 60's, and 70's, respectively.

3. BMD and RA stage

The nBMD in RA patients having stages III and IV was lower than that in patients with stages I and II in every region (two-tenths: p 0.0005, three-tenths: $p < 0.0001$, four-tenths: $p < 0.0001$). Reduction of the BMD in patients with stage III was predominant in the distal portion, as 0.2/0.4 nBMD in those patients was lower than that in the patients in other stages (p 0.01).

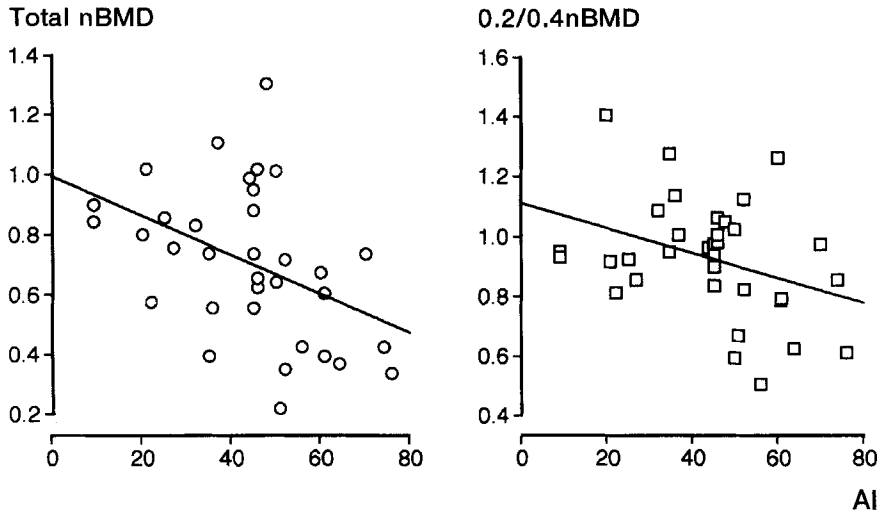

Figure 3. Relationship between total nBMD (r –0.43; p 0.01), 0.2/0.4 nBMD (r –0.36; p 0.04) and RA activity.

4. BMD and RA activity

The total nBMD in the RA patients correlated with the AI, and the 0.2/0.4 nBMD also had correlated with the AI (Figure 3). Therefore, as the AI increased, bone loss became severer, predominantly in the distal portion.

There was no correlation between the disease duration and the total nBMD (r –0.26, p 0.1).

5. BMD and corticosteroid treatment

25 patients who were given corticosteroids had a lower total nBMD (mean *SD* 0.66 *0.25*) than the patients who were not (0.84 *0.21*), but the difference was not significant (p 0.06). No relationship was found between the nBMD and the total amount of corticosteroid administered, or between the nBMD and the duration. The 0.2/0.4 nBMD was slightly lower in the patients treated with corticosteroids (0.91 *0.21*) than in those who were not (1.00 *0.14*) (p 0.2).

6. Chemical bone markers and BMD

Chemical bone markers were above the normal limit in about half of the patients, but in only a few control subjects (PTH: RA-17/control-5, ALP: RA-15/control-2, BGP: RA-8/control-5, and Hyp/Cr: RA-22/control-7). RA patients had higher PTH, ALP and Hyp/Cr values than the control subjects. The BGP values were slightly elevated in the patients (Table 1). There were no patients or control subjects who had bone markers below the normal limit. No correlation was found between the values of each bone marker and the nBMD.

Table 1. Biochemical bone markers in RA patients and control subjects. Mean *SD*

Discussion

Our investigation revealed that the decrease in the radial BMD in RA patients correlated with grip strength, RA stage and RA activity. We suggest that the inflammation and destruction of the wrist led to dysfunction of the upper extremity, accompanied by bone loss in the radius. Contrary to our expectation, there were many patients with low BMD in the proximal mid-portion of the radius, which is mainly composed of cortical bone, as well as in the distal portion, which is mainly composed of cancellous bone and is adjacent to the inflamed wrist. Several investigators (Als et al. 1985a, Peretz et al. 1989, Sambrook et al. 1990, Butler et al. 1991, Pitt et al. 1994, Lane et al. 1995) have previously reported that the distal radial BMD is reduced in RA patients. However, no regional studies have been within the radius on the BMD reduction and its affecting factors. Even if inflammation of the synovium is reduced by the natural course of the disease itself or is modified by various treatments, destruction of the wrist causes disuse of the

upper extremity. Therefore, the disuse and the high activity of RA are not always coupled. From our data, the decrease in BMD related to the increase in AI was predominant in the distal portion of the radius, while that related to the decrease in grip strength was consistent within the radius. These findings indicate that the disuse of the upper extremity has a strong effect on BMD in the whole radius, while the high activity of RA (i.e., severe inflammation of the synovium in the wrist) influences only the distal part of it. This would be supported by Shawe et al. (1993), who found a significant inverse relation between bone loss in the radial diaphysis and improvement in the physical activity index in RA patients, while that in the distal radius showed a much weaker association.

On the basis of the finding that patients in their fifties and sixties, most of whom were within 15 years postmenopausal, had the lowest BMD compared to the controls, we suggest that postmenopausal osteoporosis amplifies the bone loss in RA patients. Riggs et al. (1982) proposed that there are two forms of osteoporosis: one, postmenopausal osteoporosis, is characterized by excessive and disproportionate bone loss, involves a small subset of women in the early postmenopausal period and the other form, senile osteoporosis, characterized by proportionate bone loss involves essentially the entire population of ageing women. In other studies (Als et al. 1985b, Sambrook et al. 1986, Butler et al. 1991), bone loss in postmenopausal RA patients was greater than that in premenopausal. These observations indicate that deleterious effects of RA on BMD increased postmenopausally, perhaps predominantly in the early postmenopausal period. That would also explain the absence of a correlation between the duration of the disease and BMD. In other words, increased postmenopausal osteoporosis and the disease duration are not always parallel.

The influence of corticosteroid treatment on BMD in RA patients is controversial. Montecucco et al. (1992) have reported lower vertebral bone density in RA patients who received prednisone; it was even less than 10 mg/day. Hall et al. (1995) stated that bone resorption increased in RA patients taking low-dose steroids. However, Sambrook et al. (1986) reported that low-dose prednisone treatment did not increase the risk of generalized osteoporosis in RA patients. In our series, only 6/25 patients in the corticosteroid-treated group have ever received prednisone more than 10 mg/day. The BMD reduction in the corticosteroid-treated group tended to be larger than that in the untreated group, but the difference was not significant. We could not clarify the effect of the treatment on BMD, because of an imbalance in study population, as there were only 9 out of 34 untreated patients.

We observed a significant increase in ALP and Hyp/Cr, and a little increase in BGP levels in the RA patients. Since the markers of both bone formation and bone resorption were increased, overall bone turnover was high in our series. Several investigators (Als et al. 1985a, Gevers et al. 1986, Rico et al. 1990, Eggelmeijer et al. 1993) have reported a similar increase in bone turnover with the high levels of ALP, BGP and Hyp/Cr. They suggested that a more marked increase in bone resorption than that in bone formation was responsible for the bone loss in RA patients. We also found a significant increase in PTH levels in the RA patients, which indicated that secondary hyperparathyroidism affected the bone loss in RA patients. Van Soesbergen et al. (1986) suggested that the high bone turnover in RA patients was probably a manifestation of secondary hyperparathyroidism shown by the raised PTH levels. It has been reported that the bone-resorbing action of PTH is predominant in cortical bones (Wong 1986). However, in our study, the bone loss in patients with high PTH levels was not severer in the proximal cortical portion of the radius. Therefore, we suggest that the bone-resorbing action of PTH also influenced the distal para-articular portion with the synergistic action of cytokines produced by the inflamed synovium (Dewhirst et al. 1987, Sato et al. 1988), or was masked by other factors, such as inflammation or disuse.

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