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ORIGINAL ARTICLE

Knee deformity in rheumatoid arthritis is closely correlated with generalized osteoporosis

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Abstract To examine the relationship between knee deformity and osteoporosis in women with rheumatoid arthritis (RA), bone mineral density (BMD) in the lumbar spine and distal radius was measured using dual X-ray absorptiometry, and knee deformity (valgus or varus deformity) was measured using plain radiograms in 55 women with RA. Associations between knee deformity and BMD, disease related variables, including RA stage, RA duration, age, cumulative doses of administered glucocorticosteroids, body mass index, or postmenopausal period were evaluated. Cut-off values of the BMD defining RA patients with knee deformity were very close to the BMD value corresponding to 70% of young adult mean in the lumbar spine and distal radius. The femorotibial alignment was significantly correlated with age and deformity of the proximal tibia. Deformity of the proximal tibia was negatively correlated with the radial BMD and lumbar BMD. Deformity of the proximal tibia showed a significant difference between the groups of less than 5 years after menopause and the group of 5–10 years after menopause. We concluded that knee deformity in RA derived from deformity of the proximal tibia, and it was closely correlated with generalized osteoporosis.

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Introduction

Rheumatoid arthritis (RA) causes characteristic deformity of fingers, toes, as well as wrist and ankle joints. Although the causes of joint deformity vary with the joints, destruction of subchondral bone is considered to be an important factor of deformity in large joints, such as knee and ankle joints. In other words, bone erosion and osteoporosis weaken subchondral bone, and mechanical stress causes joint deformity by subchondral bone fracture and bone compression. Therefore, bone fragility due to generalized osteoporosis may affect joint deformity.

RA often occurs in women, and its incidence is high between the ages of 20 and 50. Recently, it has been reported that the incidence of RA has increased in elderly patients over 60. In females, it is well known that the bone mass peaks in the second decade, and rapidly decreases after menopause [1, 2]. Therefore, the conditions of joint deformity may vary with age. To evaluate the relationship between knee deformity and osteoporosis in women with RA, we examined the relationship between the degree of knee deformity observed on a frontal plane radiogram and the bone mineral density (BMD) in the lumbar spine and radius.

Patients and methods

Sixty-six female RA patients (99 knees, unilateral in 33 patients, bilateral in 33 patients) underwent total knee arthroplasty (TKA) at the Tottori University Hospital between April 1990 and March 2003. Informed consent was

obtained from all patients. Eleven patients were excluded because their radiographs were insufficient, and the remaining 55 patients (86 knees) were examined in this study. All patients satisfied the 1987 American Rheumatism Association criteria for the adult RA [3]. The age at the time of surgery ranged from 39 to 81 years (mean, 61.5 years), and the RA duration was 5–40 years (mean, 19.0 years). The Steinbrocker score [4] of the knee joint was stage 3 or more severe in all patients. All patients had been orally administered corticosteroids equivalent to 1–7.5 mg/day predonisolone for 2–40 years (mean, 15.5 years), and the cumulative dose was 1,825–54,750 mg. All patients had undergone intra-articular injection of corticosteroids irregularly before TKA, and the cumulative dose was 48–600 mg. Vitamin D_3 preparations were administered to 12 patients for 3–12 years. Estrogen and bisphosphonate preparations had not been administered. No diseases affecting bone metabolism (except for RA) were observed in all patients. The surgery was performed in 11 patients before menopause and 44 patients after menopause. The postmenopausal period was less than 5 years in 12 patients, 5–10 years in 17 patients, and more than 10 years in 15 patients.

Radiographic measurement

The femorotibial angle (FTA) was measured on preoperative weight-bearing anteroposterior radiograms of the entire lower limb (Fig. 1a). The femoral condylar-femoral shaft angle between the anatomical axis of the femur and the tangent to the subchondral plate of the femoral condyles (FCFS) and the tibial plateau-tibial shaft angle between the tangent to the subchondral plate of the tibia and the anatomical axis of the tibia (TPTS) were measured on preoperative anteroposterior radiograms of the knee joint taken in the supine position (Fig. 1b). The differences between the measurements and the means in the Japanese [5] were determined, and their absolute values ΔFTA, ΔFSTC, and ΔTPTS were regarded as parameters of knee deformity. In patients who underwent TKA of the bilateral knee joints, the measurement was performed in the knee joint with more severe deformity, and the parameters were subjected to evaluation. According to a report of Hashimura et al. [5], an FTA of 169–181° was regarded as normal in Japanese females. A knee with an FTA lower than the normal range was defined as a valgus knee, and a knee with an FTA higher than the normal range was defined as a varus knee.

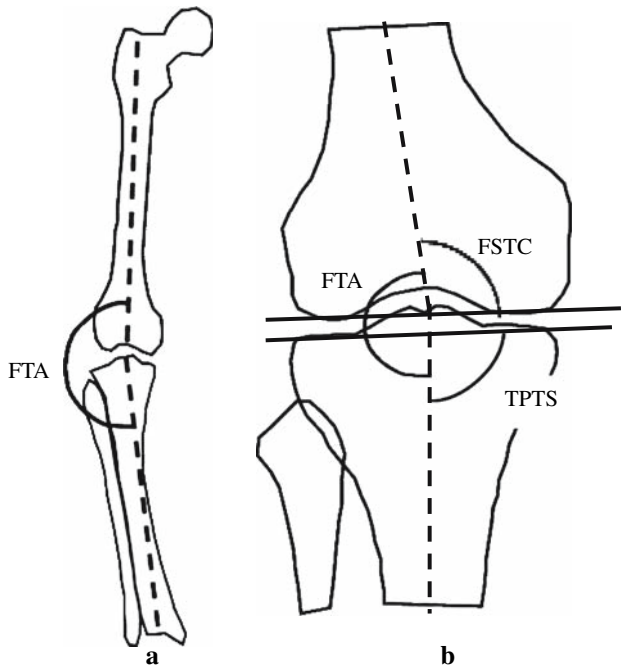

Fig. 1 Diagram of the lower limb (**a**) and the knee (**b**); femorotibial angel (FTA), femoral condylar-femoral shaft angle (FCFS), tibial plateau-tibial shaft angle (TPTS)

Bone mineral measurement

Immediately before surgery, the bone mineral density of the left radius (radial BMD) was measured at the distal 1/6 site by dual-energy X-ray absorptiometry (DXA) (DCS-600, Aloka Inc, Japan), and that of the lumbar vertebrae (L2-4) (lumbar BMD) was also measured by DXA (XR-26, Norland Inc, NJ, USA).

Statistical analysis

The relationships between the RA duration, age, BMD, cumulative doses of intra-articularly and orally administered steroids, or body mass index (BMI) and the parameters of knee deformity, and the relationships between the parameters of knee deformity were statistically analyzed using Pearson's correlation coefficients, and the *P* values were determined by the Fisher's *Z* test. The relationships between the cumulative doses of steroids and BMD were also analyzed using Pearson's correlation coefficients, and the *P* values were determined by the Fisher's *Z* test. The relationships between the postmenopausal period and parameters of knee deformity were examined by the Kruskal–Wallis test. Factors related to the parameters of knee deformity were examined by stepwise regression analysis. A P value < 0.05 was regarded as significant. Statistical analysis was performed using Statview 5.0 software (SAS Institute Inc, Cary, NC, USA). Sensitivity–specificity analysis was employed to determine cut-off values which discriminated the subjects with varus

or valgus knee deformity from those without knee deformity for the BMD of lumbar spine and radius. The cut-off values were defined as the point where the sensitivity curve intersected the specificity curve. For ROC analysis, we used StatFlex 5.0 software (Artec Inc, Osaka, Japan).

Results

Before TKA, the FTA in the 55 RA patients was distributed between 152 and 190° (mean, 176.2°). Varus deformity was observed in 22% of the patients, valgus deformity in 29%, and normal in 49% (Fig. 2).

Correlations between the parameters of knee deformity and the factors

ΔFTA was not correlated with the RA duration or BMI, but it was significantly correlated with the age and radial BMD (Table 1). There were no correlations between ΔFSTC and the factors. ΔTPTS was not correlated with the RA duration or BMI, but it was significantly correlated with the age, and radial and lumbar BMD, and slightly negatively correlated with the age (Table 1).

Relationships between the cumulative dose of steroids and the parameters of knee deformity or BMD

The cumulative dose of intra-articularly injected or orally administered steroids was not correlated with ΔFTA, ΔFSTC, ΔTPTS, or the radial and lumbar BMD.

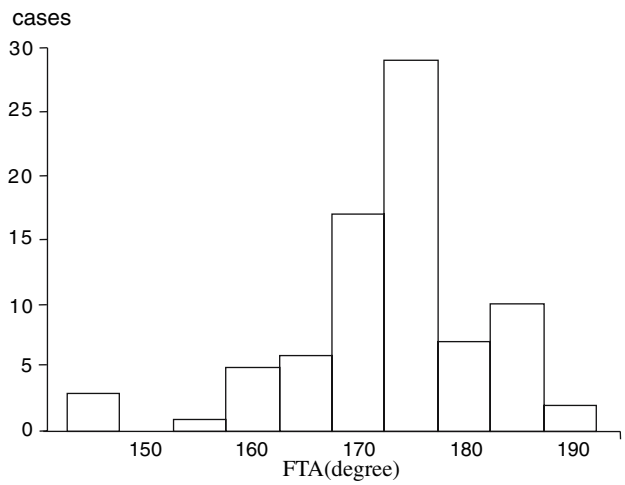

Fig. 2 Distribution of FTA

Table 1 Correlation coefficient (r) obtained by regression analysis of age, bone mineral density (BMD) and knee deformity parameters

	Age		BMD radius		BMD lumbar spine	
	r	P value	r	P value	r	P value
ΔFTA	0.50	$P < 0.05$	−0.46	$P < 0.01$	−0.13	0.65
ΔFSTC	0.01	0.91	−0.01	0.49	0.04	0.80
ΔTPTS	−0.23	$P = 0.056$	−0.49	$P < 0.01$	−0.49	$P < 0.01$

Cut-off values of the BMD defining RA women with knee deformity

At the distal radius, there was close agreement between the cut-off value (about 0.36 g/cm^2) and the BMD value corresponding to 70% of young adult mean (YAM) in Japanese women (Fig. 3). At the lumbar spine, the cut-off value (between 0.75 and 0.8 g/cm^2) was slightly higher than the value corresponding to 70% of YAM (Fig. 4).

Stepwise regression analysis of the factors involved in the parameters of knee deformity

Among the nine factors involved in ΔFTA, which were age, BMI, RA duration, radial and lumbar BMD, ΔFSTC, ΔTPTS, cumulative doses of intra-articularly and orally administered steroids, age was significantly correlated with ΔTPTS (Table 2). Among the seven factors involved in ΔTPTS, which were age, BMI, RA duration, radial and lumbar BMD, and cumulative doses of intra-articularly and

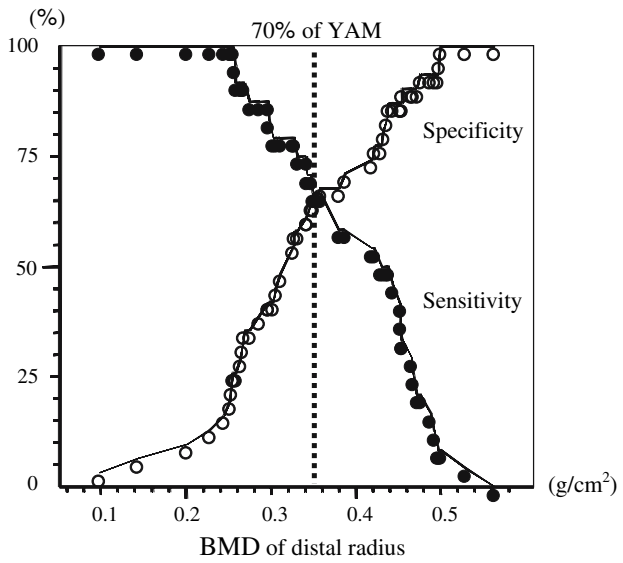

Fig. 3 Sensitivity–specificity curve for knee deformity with BMD of the radius. *Dotted line* shows 70% of YAM (young adult mean in Japanese women)

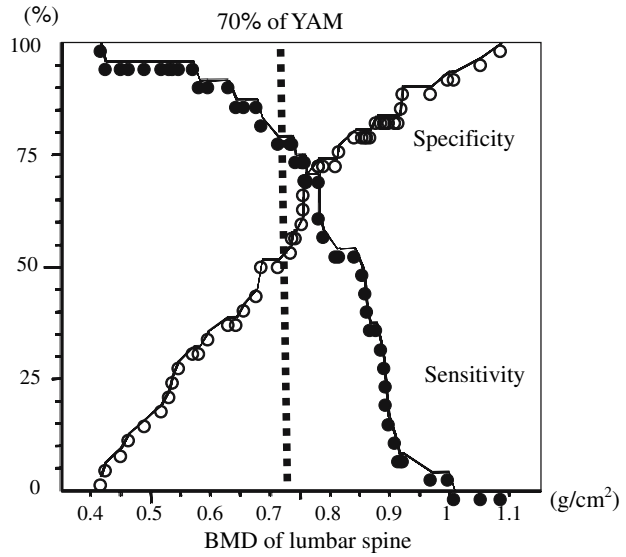

Fig. 4 Sensitivity–specificity curve for knee deformity with BMD of the lumbar spine. *Dotted line* shows 70% of YAM (young adult mean in Japanese women)

orally administered steroids, ΔTPTS was significantly correlated with the radial and lumbar BMD (Table 3).

Relationship between the parameters of knee deformity and the postmenopausal period

ΔFTA was lowest in the patients before menopause, and increased with the postmenopausal period. There were significant differences in ΔFTA and ΔTPTS between the group before menopause and the groups of 5–10 years and more than 10 years after menopause. There were also significant differences in ΔFTA between the group of less than 5 years after menopause and the groups of 5–10 years and more than 10 years after menopause. ΔTPTS also showed a significant difference between the groups of less than 5 and 5–10 years after menopause (Table 4). The mean RA duration up to TKA was 15.8 years (4–25 years) in the group before menopause, 17.7 years (9–27 years) in the group of less than 5 years after menopause, 16.9 years (5–31 years) in the group of 5–10 years after menopause, and 18.1 years (5–40 years) in the group of more than 10 years after menopause. There were no significant differences in the mean RA duration up to TKA between the groups.

Discussion

There have been a number of studies on the osteoporotic conditions in RA, but only a few studies on the relationship between osteoporosis and joint deformity. Forsblad et al. [6] published the only report showing that the degrees of deformity of finger, hand, foot, and toe joints in RA were related to the BMD in the distal radius, total femur, and femoral neck, arthritis, and duration. They stated that generalized osteoporosis affected hand and foot deformity, but they did not mention the relationship between deformity of the knee joint and such parameters. To evaluate whether generalized osteoporosis that was estimated by the BMD in the lumbar vertebrae and forearm affects the knee deformity, we performed a retrospective study on 55 female RA patients who had undergone TKA.

This study demonstrated that the degree of knee deformity in RA was significantly correlated with age and deformity of the proximal tibia (ΔTPTS), and the deformity of the proximal tibia was significantly correlated with age

Table 2 Results of stepwise regression analysis of nine factors for ΔFTA

	Step 0	Step 1	Step 2 (R = 0.688, R^2 = 0.473)		
	F value	F value	F value	rc	src
Intercept		9.250	5.014	−8.760	−8.760
Age	16.66		10.155	0.209	0.347
BMI	0.315				
Disease duration	0.177				
BMD radius	13.462				
BMD lumbar spine	4.215				
ΔFSTC	0.316				
ΔTPTS	28.615	28.615	20.737	0.677	0.496
Cumulative injected steroid dose	2.183				
Cumulative oral steroid dose	1.148				

rc regression coefficient; *src* standard regression coefficient

Stepwise regression analysis was carried out to assess the effect of independent variables on ΔFTA. A forward selection procedure with $F > 4.0$ for entry was used. Analysis was performed using Statview 5.0 software (SAS Institute Inc, Cary, NC, USA)

Table 3 Results of stepwise regression analysis of seven factors for ΔTPTS

	Step 0	Step 1	Step 2 ($R = 0.562$, $R^2 = 0.316$)		
	F value	*F* value	*F* value	rc	src
Intercept		37.372	45.523	16.951	16.951
Age	5.243				
BMI	1.306				
Disease duration	1.044				
BMD radius	15.011		5.904	−13.798	−0.309
BMD lumbar spine	16.178	16.178	6.065	−8.911	−0.338
Cumulative injected steroid dose	0.602				
Cumulative oral steroid dose	0.325				

rc regression coefficient; *src* standard regression coefficient

Stepwise regression analysis was carried out to assess the effect of independent variables on ΔTPTS. A forward selection procedure with $F > 4.0$ for entry was used. Analysis was performed using Statview 5.0 software (SAS Institute Inc., Cary, NC, USA)

Table 4 Relationship between ΔFTA, ΔTPTS, and years after menopause

Years after menopause	Number of patients	ΔFTA	ΔTPTS
None	11	2.8 ± 1.8	1.4 ± 1.2
Under 5 years	12	5.0 ± 3.0	4.1 ± 2.5
5–10 years	17	9.0 ± 6.5[a, b]	7.6 ± 6.3[a, b]
Over 10 years	15	11.4 ± 4.5[b, c]	5.7 ± 2.9[a]

Data were represented as means ± SD

[a] $P < 0.05$ versus the value in patients not having menopause

[b] $P < 0.05$ versus those who are under 5 years after menopause

[c] $P < 0.01$ versus the value in patients not having menopause

and radial and lumbar BMD. Terauchi et al. [7] reported that the degree of knee deformity in osteoarthritis (OA) was significantly correlated with the BMD in the lumbar vertebrae, and found that knee deformity occurred by micro-fracture of the subchondral bone in the medial tibial condyle due to the bone mass reduction. The cut-off value of BMD for diagnosis of primary osteoporosis is set at 70% of YAM in Japanese women. At both the lumbar spine and the distal radius, the cut-off values of the BMD defining RA women with knee deformity approximately agreed with the BMD value corresponding to 70% of YAM. Furthermore, the changes in FTA and TPTS (ΔFTA and ΔTPTS) increased with age. These results indicated that knee deformity in RA is associated with the BMD, and often occurred after menopause by deformity of the proximal tibia.

Primary osteoporosis often occurs in postmenopausal females due to estrogen deficiency. It is well known that bone mass significantly decreases in the 10 years after menopause [1, 2]. Therefore, knee deformity in RA may be accelerated by bone fragility in the proximal tibia after menopause. Furthermore, it has been shown that arthritis itself in RA is aggravated by menopause [8–11], and activation of osteoclasts by inflammatory cytokines may directly and indirectly cause bone fragility.

Since orally administered glucocorticosteroids often induce osteoporosis, it is necessary to consider them as a factor of knee deformity. It has been reported that bone mass reduction is negligible in the cortical bone of the extremities in steroid-induced osteoporosis, but it is marked in the spinal cancellous bone, and causes deterioration of the bone microstructures, resulting in a high incidence of spinal fracture. However, low-dose glucocorticosteroids (predonisolone of 10 mg/day or less) are generally administered to RA patients, and the effects of orally administered glucocorticosteroids on the bone mass in RA remain unclarified [12–15]. In the present study, orally administered corticosteroids did not affect the lumbar or radial BMD. Hvid [16] examined the bone strength of the distal femur and proximal tibia in 47 RA patients who had undergone TKA, and reported that the strength of the cancellous bone in the proximal tibia was not reduced by administration of glucocorticosteroids. Therefore, the effects of low-dose glucocorticosteroids administered to RA patients on the BMD and knee deformity are considered slight. In the present study, there was no correlation between the cumulative dose of intra-articularly administered glucocorticosteroids and knee deformity, which agreed with previous studies [17].

The present study has limitations, such as the absence of analysis of longitudinal observation, determination of the timing of TKA, indirect BMD measurement of the distal femur and proximal tibia, and no evaluation of deformity of adjacent joints, in particular, the ankle joint. Measurement of the BMD in the knee joint was considered

adequate for the purpose of this study. However, we did not perform measurement of the BMD in the knee joint because there was no reference value of BMD in the knee joint for each age group, and measurements vary widely with the region of interest [18]. Checovich et al. [19] reported that lumbar and femoral BMD were significantly correlated with proximal tibial BMD. Therefore, it is considered that lumbar BMD could predict proximal tibial BMD to some extent.

Longitudinal observation by radiography was not performed in all patients, but as shown in the typical representative case, marked knee deformity caused by collapse of the tibial condyle was observed in the patients with a low BMD after menopause. However, the patients before menopause and those with a sufficient BMD after menopause showed secondary osteoarthritic changes, such as joint space narrowing both in the medial and lateral compartment of the femorotibial joint, osteophytes and subchondral bone sclerosis (Fig. 5), and severe knee deformity was rare. In the patients with a relatively low BMD after menopause, varus or valgus knee deformity was severe (Fig. 6). The timing of TKA was determined in all patients by one of the authors (RT). As shown in the finding that there was no difference in the period from the occurrence of RA to TKA between the patients before and after menopause, early TKA was not intentionally performed in the young patients.

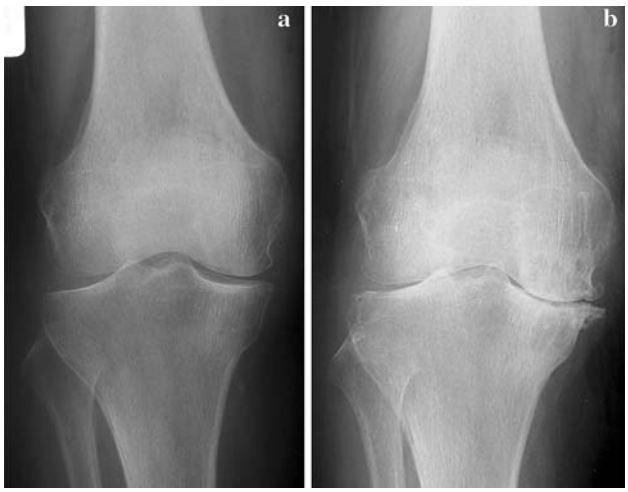

Fig. 5 Radiograms of a 60-year-old women with RA. Her lumbar BMD was 0.802 g/cm^2 (77% of YAM). **a** Knee before deformity. **b** Six years later, showing joint space narrowing both in the medial and lateral compartment of the femorotibial joint, osteophyte, and subchondral bone sclerosis

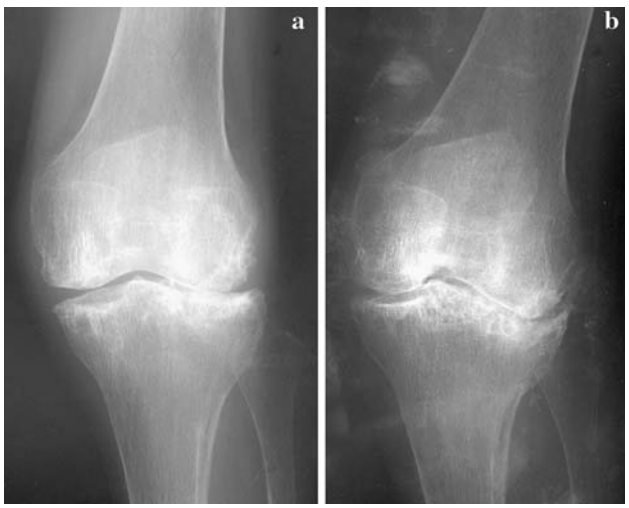

Fig. 6 Radiograms of a 60-year-old women with RA. Her lumbar BMD was 0.426 g/cm^2 (41% of YAM). **a** Knee before deformity. **b** Three years later, showing severe valgus knee deformity and collapse of lateral tibial condyle

In conclusion, knee deformity in RA was derived from deformity of the proximal tibia, and it was significantly correlated with age and BMD in the lumbar spine and radius. Therefore, it is considered that preservation of the systemic bone mineral density is necessary for prevention of knee deformity and avoiding surgery in RA.

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