incidence of seroconversion of rheumatoid factor in patients who successfully discontinued TNF inhibitors might reflect changes in immunity in patients with RA. Thus, although the studies are limited, some patients with RA may achieve a treatment holiday from TNF inhibitors, when disease course is successfully changed by intensive treatments with MTX and TNF inhibitors.

CONCLUSIONS

After the sustained remission by biologic agents targeting TNF in MTX-naive RA patients and RA patients with inadequate response to MTX, discontinuation of biologic agents is emerging from the risk/benefit point of view, including safety and economical issues. After discontinuing TNF inhibitors, patients with RA could successfully remain in low disease activity or remission without radiologic and functional damage progression of articular destruction. Such a discontinuation of TNF inhibitors is possible not only in early and active RA but also in some patients with longstanding RA. However, "deep remission," which is supposedly induced by intensive treatment using the combination of MTX and TNF inhibitors, is a prerequisite to obtain a better chance of a treatment holiday.

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CONFLICTS OF INTEREST

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ORIGINAL ARTICLE

Effects of raloxifene on lipid and bone metabolism in postmenopausal women with type 2 diabetes

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Abstract Evidence suggests that bone quality is poorer and fracture risk is higher in patients with diabetes, even those with normal bone mineral density. The aim of this study was to determine the effects of raloxifene on lipid, bone, and glucose metabolism in postmenopausal women with type 2 diabetes. The study subjects (144 postmenopausal women aged less than 80 years with type 2 diabetes) were randomly assigned into three groups: no medication, alfacalcidol 1 μg/day, or raloxifene hydrochloride 60 mg/day. The primary endpoint was the change in LDL-C at 6 months. Raloxifene significantly decreased the levels of bone metabolism markers NTX and BAP at 6 months in patients with diabetes. The primary endpoint, LDL-C at 6 months, was significantly lower in the raloxifene group than in the other two groups. However, percent changes in HDL-C were not significantly different among the three groups. Although glucose metabolism was unaffected, homocysteine, a bone quality marker, was significantly decreased at 6 months in the raloxifene group. The percent improvement in LDL-C did not correlate with percent improvement in any bone metabolism or bone quality markers. Raloxifene, unlike estrogen, improved LDL-C and decreased homocysteine, indicating that raloxifene can potentially improve LDL-C as well as bone quality in postmenopausal women with type 2 diabetes.

Keywords Raloxifene · Type 2 diabetes · Lipid metabolism · Bone metabolism · Bone quality

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Introduction

Type 2 diabetes mellitus is a major lifestyle disease, a category in which osteoporosis has also been recently included. The numbers of patients with diseases such as diabetes and osteoporosis, and the risk of cardiovascular events, are growing rapidly. Moreover, because the growth of menopause-associated osteoporosis is a major concern in women, a comprehensive follow-up that takes into account osteoporosis and arteriosclerosis is important. Because osteoporosis is common in patients with diabetes, the importance of the management of osteoporosis has been highlighted in recent years, but the true picture regarding diabetes-associated abnormalities of bone metabolism remains unclear.

Conventionally, the risk of fracture was believed to be determined by bone mass and bone mineral density, but in metabolic diseases such as diabetes, which is associated with bone fragility, the concept of bone quality rather than bone mass has been emerging [1]. For instance, it is reported that the relative risk of proximal femoral fracture is higher in type 2 diabetes, even when bone mineral density is within the normal range, and thus decreased bone quality, which affects bone strength other than bone mineral density, has come under the spotlight [2, 3]. In rat models with spontaneous diabetes, abnormal cross-linking of collagen is involved in decreased bone strength, acting through a mechanism independent of bone mineral density [4].

However, precise mechanisms regarding the impairment of bone quality in diabetes remains unknown.

Numerous drugs are currently available for treatment of osteoporosis, among which raloxifene hydrochloride, a selective estrogen receptor modulator (SERM), lowers the risk of fracture by increasing bone mass and improves bone quality by enhancing collagen cross-linking in a rabbit model [5, 6]. It is noteworthy that raloxifene also improves lipid metabolism [7]. Because raloxifene is supposed to possess pleiotropic effects, it can be postulated that raloxifene affects not only bone metabolism but also lipid or glucose metabolism. However, effects of raloxifene on such multiple metabolisms are yet to be elucidated, providing the motivation for our present research. Therefore, we here assessed effects of raloxifene on metabolisms of lipid, glucose, and bone in patients with type 2 diabetes mellitus.

Materials and methods

Study population

The subjects of this research were women at least 2 years postmenopausal with type 2 diabetes, less than 80 years of age, who were current patients of the First Department of Medicine at the University of Occupational and Environmental Health, Japan, and its associated centers from October 2005 to September 2010. Patients with a history of or currently suffering venous thromboembolism, with long-term immobility, patients with history of hypersensitivity to any of the components of raloxifene, and patients receiving any drugs that affect bone metabolism (bisphosphonates, vitamin K, estrogen, calcium, anabolic steroids, or male/female hormones) were excluded from the research. Patients with triglycerides (TG) concentration of 400 mg/dl or higher were also excluded.

This research was approved by the ethics committee in centers participating the study, and informed consent was obtained from all subjects (UMIN 000004399).

Study protocol

Patients were randomly assigned into three groups: no medication (control), alfacalcidol 1 μg/day (alfacalcidol group), or raloxifene 60 mg/day (raloxifene group). Before the start of treatment and after 6 months, total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), TG, HbA1c, fasting plasma glucose (FPG), fasting plasma insulin (FPI), serum N-terminal telopeptide of type I collagen (NTX), bone-specific alkaline phosphatase (BAP), homocysteine, and pentosidine were measured under fasting conditions, and the values measured or calculated at 6 months were compared with those at baseline. No changes were allowed during the study period in drugs that might affect lipid metabolism or glucose metabolism.

Efficacy and safety assessments

The primary endpoint was a change in LDL-C after the 6-month therapy. The secondary endpoints were changes in TG, serum NTX, BAP, homocysteine, and pentosidine after the 6-month therapy.

Measurements of biochemical variables

Before the start and after the 6-month treatment, fasting blood samples were withdrawn in the morning. TC, HDL-C, TG, HbA1c, FPG, and FPI were measured rapidly using standard techniques. LDL-C was calculated according to the Friedewald formula from the results for TC, HDL-C, and TG [LDL-C + TC − (HDL + TG/5)]. As measures of bone metabolism, the bone formation marker, BAP, and bone resorption marker, serum NTX, were determined. BAP was measured using an enzyme immunoassay technique (Osteolinks BAP; Quidel Corporation, San Diego, CA, USA; fully automated EIA apparatus, Nippon Advanced Technology) and serum NTX was determined using an enzyme-linked immunosorbent assay (Osteomark NTX Serum, Inverness Medical Japan; fully automated EIA apparatus, Nippon Advanced Technology). As a measure of bone quality, homocysteine was determined using high performance liquid chromatography (YMC-Pack Pro C18; YMC, HPLC system/Shimadzu Corporation, Hitachi, JASCO Corporation, Japan) and pentosidine was determined using an enzyme-linked immunosorbent assay kit (FSK pentosidine; Fushimi Pharmaceutical, Benchmark 1575 Microplate Reader; Sakura Seiki).

Statistical analysis

Analyses were performed using the PASW Statistics 18.0 software package. Data were expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) and Tukey's test were used to compare the three groups. The Wilcoxon test was used for within-group comparisons versus baseline. The Spearman rank correlation coefficient was used to determine correlations. Differences with $p < 0.05$ were regarded as significant.

Results

Patient demographics

One hundred forty-four patients with postmenopausal type 2 diabetics met the enrollment criteria and gave informed

consent to participate in this research. Each patient was randomly assigned to each treatment arm, yielding 51 patients in the control group, 48 in the alfacalcidol group, and 45 in the raloxifene group. In the control group, 7 patients violated the protocol for reasons such as change in anti-diabetic drugs because of worsening of diabetes, and 7 patients dropped out by failure to return to the study site. In the alfacalcidol group, 1 patient dropped out because of palpitation and 4 patients from failure to return. In the raloxifene group, 1 patient dropped out because of edema, 1 from feeling unwell, 1 from attacks of lower leg spasm, and 1 because of failure to return. Thus, the study groups comprised 37 patients in the control group, 43 in the alfacalcidol group, and 41 in the raloxifene group. The characteristics of the patients are presented in Table 1. Before the start of treatment, there were no differences among the three groups in height, body weight, or body mass index (BMI), or in the numerical measures of lipid metabolism, glucose metabolism, bone metabolism, or bone quality.

Bone metabolism

First, we investigated the effects of raloxifene on bone metabolism markers. BAP, a bone formation marker, was unchanged in the control group, but decreased significantly at 6 months after the treatment in both the alfacalcidol and raloxifene groups (Fig. 1a). However, the percent changes in BAP were not significant (Fig. 1e). Similar to BAP, the bone resorption marker serum NTX was unchanged in the control group but significantly and markedly decreased at 6 months in both alfacalcidol and raloxifene groups (Fig. 1b). The percent changes in serum NTX in the raloxifene group (-17.8 ± 23.8 %) were significantly higher than in the control group (-3.4 ± 18.9 %, $p = 0.022$) (Fig. 1f). These findings showed that raloxifene significantly reduced both BAP and serum NTX, compared to the control, confirming that this product has a fundamental lowering effect on bone metabolic turnover.

Table 1 Baseline characteristics of postmenopausal women with type 2 diabetes mellitus randomized to treatment with control, alfacalcidol, or raloxifene

Factor	Control ($n = 37$)	Alfacalcidol ($n = 43$)	Raloxifene ($n = 41$)	p value
Age (years)	66.9 ± 7.4	66.2 ± 7.3	66.5 ± 7.1	NS
BH (cm)	150.5 ± 5.0	150.0 ± 5.4	150.8 ± 5.5	NS
BW (kg)	55.1 ± 8.3	53.6 ± 8.3	52.3 ± 7.7	NS
BMI (kg/m^2)	24.3 ± 3.4	23.9 ± 3.7	23.0 ± 3.1	NS
SBP (mmHg)	135.8 ± 17.8	133.3 ± 17.7	134.6 ± 14.6	NS
DBP (mmHg)	73.2 ± 11.0	73.8 ± 10.6	74.4 ± 8.3	NS
TC (mg/dl)	208.2 ± 23.1	202.2 ± 32.3	201.2 ± 28.8	NS
LDL-C (mg/dl)	120.3 ± 20.9	119.2 ± 33.0	115.4 ± 22.2	NS
HDL-C (mg/dl)	59.8 ± 14.3	59.6 ± 14.7	63.6 ± 18.9	NS
TG (mg/dl)	110.6 ± 48.7	124.0 ± 51.4	111.0 ± 55.7	NS
HbA1c (%)	6.9 ± 1.1	7.2 ± 1.0	6.8 ± 0.9	NS
FPG (mg/dl)	137.7 ± 25.2	133.8 ± 30.1	129.2 ± 23.5	NS
FPI (μU/ml)	7.4 ± 3.0	6.4 ± 3.2	5.5 ± 3.1	NS
BAP (IU/l)	29.9 ± 13.2	29.1 ± 9.0	31.1 ± 11.3	NS
s-NTX (nmol BCE/l)	16.2 ± 3.4	15.8 ± 4.3	16.4 ± 4.8	NS
Homocysteine (μmol/l)	9.9 ± 3.4	8.1 ± 2.2	9.0 ± 2.7	NS
Pentosidine (μg/ml)	0.06 ± 0.02	0.06 ± 0.02	0.07 ± 0.05	NS
Pioglitazone	14 (37.8)	18 (41.9)	16 (39.0)	NS
Metformin	15 (40.5)	16 (37.2)	15 (36.6)	NS
ACE inhibitors or ARBs	20 (54.1)	24 (55.8)	21 (51.2)	NS
Statins	14 (37.8)	14 (32.6)	16 (39.0)	NS

Data are expressed as mean ± SD or n(%)

NS not significant, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein-cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *TG* triglycerides, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *BAP* bone-specific alkaline phosphatase, *s-NTX* serum n-telopeptide, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blockers

p values are based on one-way analysis of variance (ANOVA), comparison of the three groups

Lipid profile

Next, we investigated the effect of raloxifene on lipid metabolism, which is the main objective of this research. Serum levels of LDL-C were significantly decreased in the raloxifene group during 6 months of treatment, whereas those in the control and alfacalcidol groups did not change, (Fig. 1c). The percentage decrease in LDL-C in the raloxifene group was significantly higher than that in the control group at 6 months (Fig. 1g). Therefore, this study was satisfied with the primary endpoint that raloxifene reduced serum levels of LDL-C within 6 months. In contrast, significantly higher serum levels of HDL-C were noted only in the alfacalcidol group during the 6 months of treatment (Fig. 1d). The percent changes in HDL-C levels were not significantly different among the three groups (Fig. 1h). There was no significant difference in TG concentrations between the alfacalcidol and raloxifene groups, although these levels tended to increase in the control (Fig. 1i, l).

Glucose metabolism

There were no significant changes in HbA1c, FPG, or FPI in the control group, alfacalcidol group, or raloxifene group.

Bone quality

Finally, we evaluated the effect of raloxifene on homocysteine, a marker of bone quality. Serum levels of

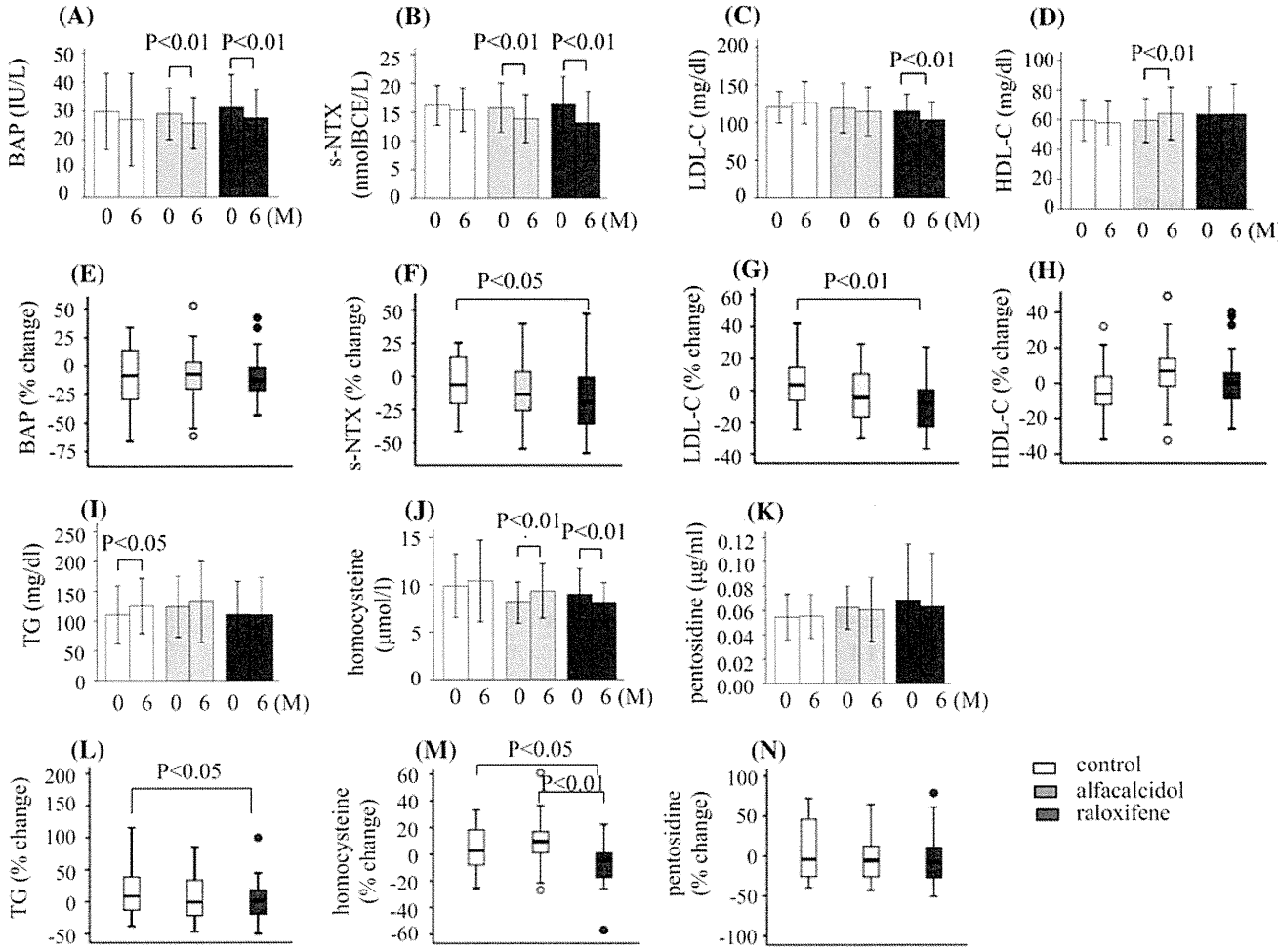

Fig. 1 Effect of 6-month treatment with alfacalcidol, raloxifene, and control on bone-specific alkaline phosphatase (**a**), serum N-terminal-telopeptide of type I collagen (s-NTX) (**b**), low-density lipoprotein-cholesterol (LDL-C) (**c**), high-density lipoprotein-cholesterol (HDL-C) (**d**), triglycerides (TG) (**i**), homocysteine (**j**), and pentosidine (**k**). Comparison of percent changes in bone-specific alkaline phosphatase (**e**), serum n-telopeptide (**f**), LDL-C (**g**), HDL-C (**h**), TG (**l**), homocysteine (**m**), and pentosidine at 6 months (**n**) between control, alfacalcidol, and raloxifene. Data are mean ± SD (**a–d**, **i–k**). Data are depicted as *box-and-whisker* plots showing medians, 25th and 75th quartiles, and complete data range (**e–h**, **l–n**). *White bars* and *white boxes* indicate control; *gray bars* and *gray boxes* indicate alfacalcidol; *black bars* and *black boxes* indicate raloxifene. Intergroup differences were analyzed by Wilcoxon matched-pairs test. Differences between groups were analyzed by one-way analysis of variance (ANOVA) using the Tukey multiple comparison test

homocysteine markedly and significantly decreased in the raloxifene group, and it is noteworthy that the percent decrease in serum homocysteine was significantly higher than that in control and alfacalcidol groups (Fig. 1j, m). In contrast, pentosidine levels did not change significantly in any group (Fig. 1k, n).

There was no correlation between the percent changes in LDL-C, HDL-C, and TG from 0 to 6 months after the treatment with raloxifene and those in serum levels of BAP, NTX, homocysteine, and pentosidine. There was also no correlation between the percent changes in homocysteine by raloxifene therapy and those in TC, LDL-C, HDL-C, and TG. To summarize, the improvements in LDL-C and homocysteine produced by raloxifene were independent of the changes in bone metabolism markers, suggesting different sites of action for raloxifene.

Discussion

In the present study, treatment with raloxifene, a member of the SERM family of drugs, produced a decrease in s-NTX of at least 15 % after 6 months in postmenopausal patients with type 2 diabetes mellitus, whereas the absolute values of s-NTX and BAP remained normal ranges for premenopausal women during 6 months, implying that raloxifene regulates bone remodeling by suppressing high bone metabolic turnover without excessively inhibiting bone formation. Decreased bone mass and bone fragility are reported as potential causes of fractures in type 1 diabetes through decreased bone formation associated with impaired insulin secretion [8]. However, although a meta-analysis by Vestergaard [2] showed that the risk of femoral neck fracture is increased by 1.38 (range, 1.25–1.53) in type 2 diabetics, there is little information on bone turnover in animal models of type 2 diabetes and in type 2 diabetic patients. In the MORE and bridging studies, serum BAP as well as u-CTX and u-NTX decreased in patients with type 2 diabetes treated with raloxifene [5, 9].

One of the remarkable results of the present study was that raloxifene significantly reduced serum levels of homocysteine, a major content of cross-linked advanced glycation end products (AGEs), in postmenopausal women with type 2 diabetes, reflecting improvement in bone quality. The fracture risk is higher in Japanese women with type 2 diabetes, even when bone mineral density is high [10]. In other words, bone mineral density has a minor role in increased risk of fracture in type 2 diabetes, and factor(s) other than bone mineral density could determine bone strength, i.e., bone quality. The methods for noninvasive and objective evaluation of bone quality are still only exploratory. The content of AGEs in the bone was associated with the decrease of bone strength in animal models of diabetes, and the serum level of AGE pentosidine was associated with the incidence of fracture in Japanese women with type 2 diabetes [11]. AGEs stimulate cell death by interfering with differentiation and maturation, and with production of interleukin-6 in osteoblasts, implying a potential to enhance bone resorption [12, 13].

However, it is also evident that AGEs can cause impairment of bone metabolism, that abnormal cross-linking of collagen in bone is noticed in patients with osteoporosis and hyperhomocysteinemia, and that serum levels of AGEs are associated with deterioration of bone quality in patients with diabetes [14]. In these contexts, reduction in blood levels of pentosidine and other AGEs is necessary to improve bone quality. In the EVA clinical study in which raloxifene was compared with alendronate, it was revealed that raloxifene was involved in the improvement of bone quality [15]. In the present study, treatment with raloxifene significantly lowered serum homocysteine although it did not affect serum pentosidine levels. Raloxifene is reported to have no adverse impact on glucose metabolism [16], and in the present study no major effects of raloxifene on blood glucose levels, insulin resistance, or other indicators of glucose metabolism were observed. Taken together with our current results, raloxifene, in contrast to bisphosphonates, decreases cross-linking of bad AGE contents, such as homocysteine, rather than increasing the physiological cross-links of collagen in bone, resulting in improvement of bone quality in patients with type 2 diabetes, in whom deterioration of bone quality is thought to be a causal factor of bone fractures.

It is well known that raloxifene possesses pleiotropic effects. However, the effects of raloxifene on lipid metabolism remain unclear, especially in patients with diabetes. In the present study, postmenopausal patients with diabetes were treated with raloxifene, and a significant decrease in LDL-C levels was noted without adversely affecting glucose metabolism. It was reported that blood levels of cholesterol are elevated in ovariectomized rats, but a decrease in cholesterol was noted in these rats after treatment with estrogen [17], which might lead to reduction in cardiovascular events with estrogen treatment in postmenopausal women. However, the Women's Health Initiative (WHI) study reported that hormone replacement therapy (HRT) using estrogen increases the risk of coronary artery disease and cerebral infarction [18]. Nevertheless, in the Raloxifene Use for The Heart (RUTH) trial, raloxifene did not increase the risk of cardiovascular events in elderly women at risk for coronary artery disease [7]. Furthermore, the MORE study of 4-year treatment with raloxifene indicated that raloxifene significantly reduced the number of new cases of cardiovascular disorders in patients with several risk factors [19]. The results of the present study showed a significant decrease in LDL-C

following the 6-month treatment with raloxifene in patients with diabetes, without any increase in HDL-C or decrease in TG. In addition, because there was no correlation between the percent improvement in bone metabolism or bone quality markers and the percent improvement in lipid metabolism, it is possible that the beneficial effect of raloxifene on lipid metabolism is manifested through a mechanism different from its effects on bone metabolism and bone quality. Hypercholesterolemia is a risk factor for arteriosclerosis, and in the United Kingdom Prospective Diabetes Study (UKPDS) conducted in patients with type 2 diabetes, the leading risk factor of coronary artery disease events was actually LDL-C [20]. Based on the present results, raloxifene treatment produced a significant fall in LDL-C without adversely affecting glucose metabolism, indicating that raloxifene is potentially useful for inhibiting arteriosclerosis in diabetes patients.

The results of the present study showed a significant increase in HDL-C by the 6-month treatment with alfacalcidol in diabetic patients. The mechanism thereof is still unclear; however, vitamin D was involved in adipocyte differentiation via peroxisome proliferator-activated receptor-gamma (PPAR-γ) and retinoid X receptor (RXR) [21, 22], wherein it is speculated that PPAR-γ accelerated ABCA1 expression in the liver or macrophages, promoted cholesterol emission, and increased HDL-C [23]. Moreover, recently, Shab-Bidar et al. [24] also reported that HDL-C increased, depending on the levels of vitamin D. On the other hand, homocysteine also significantly increased according to the application of alfacalcidol. The connection between vitamin D and homocysteine is not clear at present, and no reports in terms of the mechanism thereof can be found in the literature. It is unclear why homocysteine increased according to vitamin D in this study, however, considering that pentosidine did not increase on vitamin D.

Osteoporosis is especially common in postmenopausal women, and because it is evident that the risk of fracture is increased by deterioration of bone quality in patients with type 2 diabetes, osteoporosis is becoming an important community concern with the progressive aging of the society. Raloxifene improves LDL-C, bone metabolism, and bone quality without adversely affecting glucose metabolism. Therefore, raloxifene may be suitable as a comprehensive healthcare option for the inhibition of arteriosclerosis and protection against bone fractures in postmenopausal patients with type 2 diabetes.

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A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study

In terms of the relationship between synovial inflammation and radiographic changes, including both joint damage repair and progression,[1] in rheumatoid arthritis (RA), pre-existing joint damage and persistent synovitis may promote joint destruction, while in the absence of synovitis, damaged joints may heal.[2 3] Although presentation of radiographic results using cumulative probability plots has substantially improved understanding of clinical trial data,[4] the effects of treatments on radiographic progression and improvement (regression) in individual RA patients has not yet been fully explained.

In the JESMR study,[5 6] 151 active RA patients unresponsive to treatment with methotrexate (MTX) were randomised into 1 of 2 treatment groups: etanercept (ETN) 50 mg/week with 6–8 mg/week of MTX (the E+M group), or ETN alone (the E group). Radiographs of the hands and feet before ETN (baseline) and during the first year of treatment were available from 53 (72%) and 68 (88%) patients in the E and E+M groups, respectively. Baseline characteristics of patients were comparable between those with and without available radiographic data in each treatment group (data not shown). However, most patients without data did not complete the study up to Week 52 as per protocol, chiefly due to lack of efficacy in the E group.[6] The mean baseline total Sharp-van der Heijde score (TSS)[7] was 114.5 in the E group and 113.1 in the E+M group (disease duration: 10.0 years and 8.4 years, respectively), and the smallest detectable change (SDC) in TSS over 52 weeks was 1.9.

Cumulative probability plots provided by the American College of Rheumatology (ACR)-N[8] clearly demonstrated a superior response (figure 1A,B) and a significantly greater ACR50 response rate in the E+M group at week 52 (76.5% vs 50.9%, p=0.0041, Fisher's exact test). Merged probability plots of individual radiographic change over 52 weeks (ΔTSS) suggested preferential existence of aggressive radiographic progressors among ACR50 non-responders in the E group. The relationship among treatment, clinical disease activity, and radiographic change was further addressed using time-averaged disease activity score of 28 joints (DAS28) over 52 weeks in place of ACR-N at Week 52 (figure 1C,D). Significant correlation between time-averaged DAS28 and ΔTSS was observed in the E (r^2=0.097, p=0.023) but not the E+M group (r^2=0.019, p=0.26). Aggressive radiographic progression was preferentially observed among patients with moderate or high activity on average in the E group (figure 1C), while in the E+M group, radiographic progression among these patients seemed to be balanced by radiographic regression among those in remission or with low disease activity (figures 1D–F).

The absence of radiographic regressors (>SDC) among clinical responders in the E group (figure 1A,C,E) was surprising, although 18.2% of those patients showed regression within the SDC. This may be partly explained by the limitations of the study due to the small number of patients involved. Another limitation was much lower MTX dose at study enrolment than the current global standard dosage: 7.0±1.4 (the mean±SD) and 7.4±1.1 in the E and E+M groups, respectively.

In summary, we first demonstrated the relationship between individual clinical responses and radiographic changes by merging cumulative probability plots of ACR-N or time-averaged DAS28 and ΔTSS. These presentations clearly show the relationships between two parameters as a whole, facilitating further post hoc analyses of clinical trials. Further, merged presentation of probability plots is useful in comparing a single parameter (eg, health assessment questionnaire-disability index: HAQ-DI) before and after treatments (figure 2). However, merged presentation of probability plots must be followed by statistical analyses after being classified into binary or ternary categories, as we showed here.

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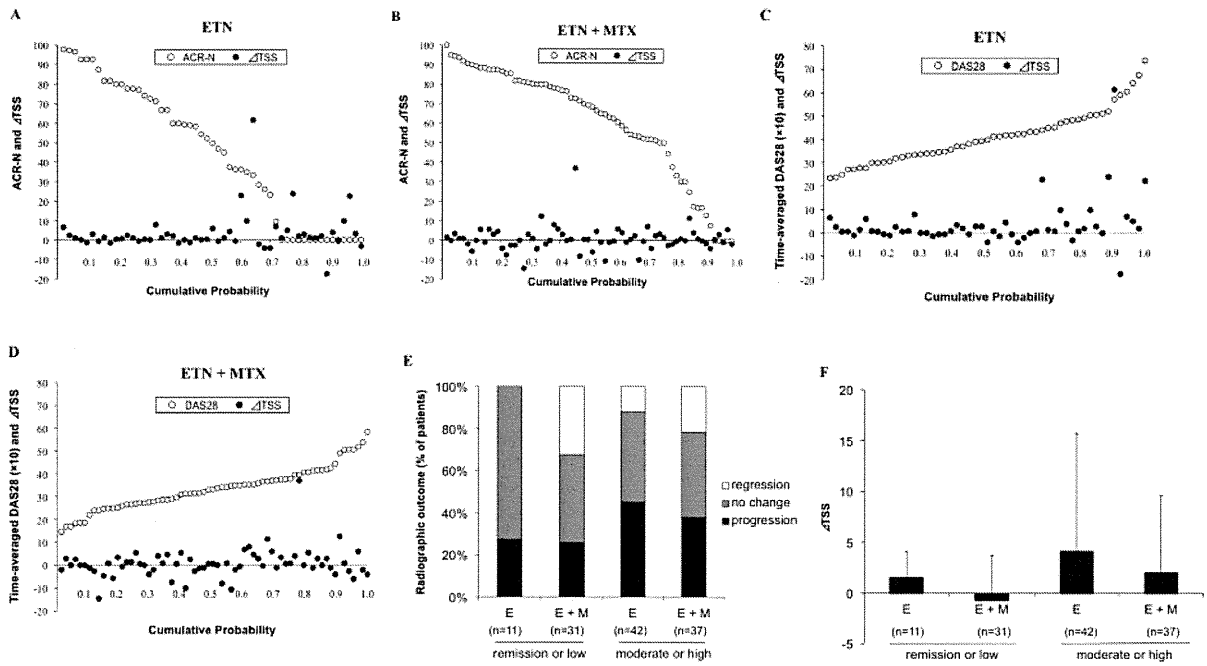
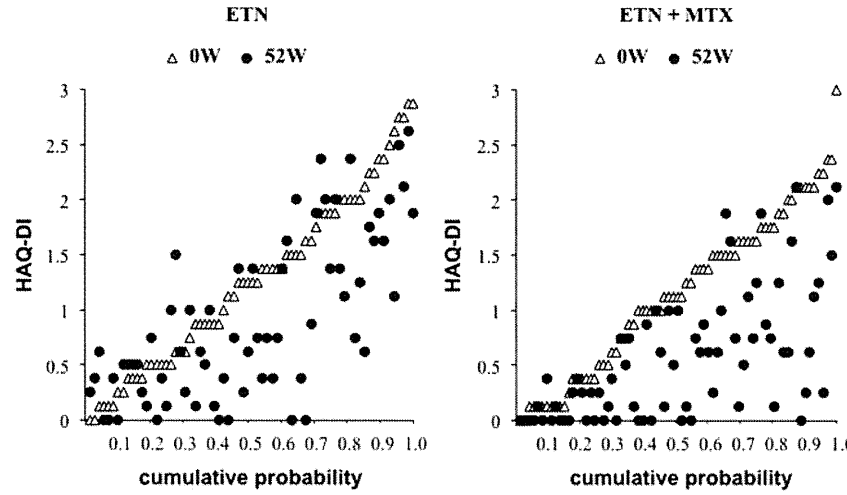


Figure 1 Cumulative probability plot analysis of ACR-N (A,B) or time-averaged DAS28 (C,D) and radiographic changes in the E (A,C) and E+M groups (B,D), merged to keep same patients on the vertical line, followed by the radiographic outcomes (E) and changes (F) stratified by the treatment and time-averaged disease activity state. Time-averaged DAS28 was calculated by the area under the curve of DAS28 at weeks 0, 2, 4, 8, 12, 24 and 52, divided by 52. No significant differences were observed between groups using Pearson's test (E) and Kruskal-Wallis test (F). ACR, American College of Rheumatology; DAS28, disease activity score of 28 joints; ETN, etanercept; MTX, methotrexate; TSS, total Sharp-van der Heijde score.



Merged probability plots of individual health assessment questionnaire-disability index (HAQ-DI) scores at baseline (open triangle) and Week 52 (closed circle) in the E (left) and E+M groups (right). Subsequent analyses included comparison of the rate of HAQ-DI≤0.5 at 52 weeks in patients with baseline HAQ-DI>1.5. None of 15 patients (0.0%) in the E group and 6 of 23 patients (26.1%) in the E+M group, respectively; p=0.037 by Fisher's exact test (one-sided). ETN, etanercept; MTX, methotrexate.

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A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study

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CLINICAL IMAGING

Diagnosis of early-stage rheumatoid arthritis: usefulness of unenhanced and gadolinium-enhanced MR images at 3 T

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Abstract

Forty-one consecutive unclassified arthritis patients with polyarthralgia including wrist joint were evaluated with 3-T MRI as possible early-stage rheumatoid arthritis (RA). After prospective follow-up, 21 of 41 patients fulfilled the American College of Rheumatology (ACR) criteria. Synovitis was detected in all 21 RA patients (sensitivity=100%) with postcontrast MRI and in 14 patients (67%) with unenhanced MRI when none of them fulfilled ACR diagnostic criteria. Fat-suppressed intermediate-weighted fast spin-echo (FSE) image showed high detection rate of synovitis and bone erosion, whereas FIESTA image clearly delineated joint fluid and bone trabeculae. MRI at 3 T is a potentially powerful tool for discriminating and managing early-stage RA patients.

Keywords: 3 T MRI; Rheumatoid arthritis (RA); Arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing synovial joint damage, disability, and a shortened life expectancy. Recognition of RA as early as possible is crucial, because a significant proportion of the patients develop irreversible joint damage shortly after disease onset [1]. Early intervention with nonbiological or biological disease-modifying antirheumatic drugs (DMARDs) is very important for the control of both synovitis and bone destruction. Recently, American College of Rheumatology (ACR) 2008 recommendations for the use of nonbiologic and biologic DMARDs in RA have been reported [2]. The use of an antitumor necrosis factor agent in combination with methotrexate was recommended if high disease activity was present for even less than 3 months with features of both a poor prognosis and an absence of either barriers related to treatment cost and no insurance restrictions to accessing medical care. This decision was supported by the results of pharmacoeconomic evaluations conducted on UK populations [3]. To initiate early aggressive therapy, reliable and rapid determination of diagnosis is required.

ACR 1987 revised criteria, which are based on clinical manifestations and radiographic findings, are commonly used for disease diagnosis. Although the ACR criteria reach a sensitivity of 90% if patients are observed over a period of several years, this cumulative approach has been shown to be insufficient for early diagnosis of RA in patients with arthritis of recent onset (sensitivity 50–70%) [4].

Three-tesla MRI can visualize musculoskeletal structures more clearly than 1.5-T MRI due to the enhanced signal-to-noise ratio (SNR) and the higher spatial resolution, and has the potential to improve diagnostic abilities in the musculoskeletal system including the hand [5]. Wieners et al. [6] reported that the MR image quality of RA hands is better at 3 T than at 1.5 T; however, there remains about the value of 3-T MRI in patients

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with undifferentiated arthritis, which is defined as early arthritis that does not fulfill the classification criteria for a more definitive diagnosis [7]. The purpose of this study was to evaluate the diagnostic ability of unenhanced and postcontrast MRI at 3 T for the early-stage RA.

2. Materials and methods

2.1. Study population

This study was approved by our institutional review board. Forty-one consecutive patients (5 men and 36 women; age range, 26–84 years; mean age, 59 years) between January 2006 and March 2007 were prospectively included in the study; the patients fulfilled all of the following criteria: (a) clinically possible early-stage RA and had presented with polyarthralgia including wrist joint, (b) without radiographic evidence of RA, and (c) not fulfilled with four or more ACR 1987 diagnostic criteria. Informed consent was obtained from every patient prior to enrollment in the study. A standard diagnostic evaluation including laboratory testing was performed at the first visit. All patients underwent posteroanterior and oblique hand radiographs before MRI. The mean interval between MRI and radiography was 5 days (range, 0–14 days). One musculoskeletal radiologist assessed the radiographs, and one rheumatologist judged the ACR criteria conclusively.

2.2. MRI Protocol

MRI was performed with a 3-T MRI unit (Signa 3T, General Electric Healthcare, Milwaukee, USA) and either an eight-channel receive-only coil or two 3-in. round surface coils. The patients underwent imaging in a prone position, with arms semiflexed above the head and hands positioned in the center of the coil. First, coronal unenhanced images of unilateral more symptomatic wrist joint were obtained, and then the entire structure of the bilateral hands including the distal radioulnar joint and the distal interphalangeal joints was evaluated by contrast-enhanced images.

For coronal unenhanced images, two 3-in. round surface coils and the following pulse sequences were used: intermediate-weighted fast spin-echo (FSE) with fat saturation [repetition time (ms)/echo time (ms)=2000/18.4, flip angle 90°, matrix size of 320×256, acquisition time 5:48 min], and imaging and fast imaging employing steady-state acquisition (FIESTA) imaging [repetition time (ms)/echo time (ms)=8/2.3, flip angle 50, matrix size of 288×288, acquisition time 2:30 min]. The field of view was 8 cm and the thickness was 2 mm.

Contrast-enhanced images were obtained after a bolus injection of 0.1 mmol/kg gadoteridol (ProHance; Eisai, Tokyo, Japan) into a vein in the contralateral arm. A fat-suppressed T1-weighted spin-echo sequence [repetition time (ms)/echo time (ms)=800/11, 3 mm section thickness, matrix size of 512×512, field of view of 24 cm] and an eight-channel receiver coil were used for postcontrast image.

2.3. MRI Evaluation

Two radiologists with over 10 years of experience (T.A., Y.Y.) reviewed the images in consensus for the presence of synovitis, bone erosion, and tenosynovitis without knowledge of personal identity and clinical findings. Synovitis was defined as a region of the synovial compartment showing excessive contrast enhancement on postcontrast images or an increase in the thickness of the synovial membrane on unenhanced images. Bone erosion was considered to be a sharply delineated juxta-articular lesion with a cortical defect. Tenosynovitis was defined as a contrast enhancement or an increase in the thickness of the tendon sheath.

2.4. Follow-up procedures

Clinical follow-up of the patients was continued until a definitive diagnosis was made. After prospective follow-up of more than 1 year, the diagnosis of RA was confirmed by one rheumatologist according to the ACR criteria. The average follow-up from MRI to the final clinical visit was 892 days (range, 372–1385 days). Patients lost to follow-up for unknown reasons were excluded from analysis.

2.5. Statistical analysis

A Fisher's exact probability test was used to compare the two groups in terms of the percentages of patients who had synovitis, bone erosion, or tenosynovitis. All statistical analyses were performed with StatView 5.0 (SAS Institute). P values less than .01 were considered significant in all analysis.

3. Results

After clinical follow-up, 37 of 41 patients had a confirmed diagnosis: 21 patients had RA and 16 had a non-RA disease. The final clinical diagnoses for the non-RA cases were as follows: osteoarthritis (n=3), systemic lupus erythematosus (n=3), Sjögren syndrome (n=2), remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome (n=2), dermatomyositis (n=1), polymyalgia rheumatica (n=1), and unclassified self-limited arthritis (n=4). Three patients were lost to follow-up and one patient has not obtained final diagnosis during follow-up periods. Rheumatoid factor was positive in 11 (52%) of 21 RA patients and in 5 (31%) of 16 non-RA patients.

3.1. Unenhanced MRI findings

Frequencies of synovitis, bone erosion, and tenosynovitis between two groups on two unenhanced images are

Table 1
Unenhanced MR findings for differentiation between early RA and non-RA

MR Findings	Early RA (n=21)	Non-RA (n=16)	P value
Intermediate-weighted FSE with fat saturation			
Synovitis	14 (67%)	3 (19%)	<.01
Bone erosion	12 (57%)	1 (8%)	<.01
Tenosynovitis	9 (43%)	2 (13%)	.07
Fast imaging employing steady-state acquisition			
Synovitis	12 (57%)	2 (13%)	.070
Bone erosion	11 (52%)	1 (7%)	<.01
Tenosynovitis	7 (33%)	2 (13%)	.250

summarized in Table 1. The detection rates of the fat-suppressed intermediate-weighted FSE were 67% (14/21) for synovitis and 57% (12/21) for bone erosion in the early RA; the early RA patients had significantly higher positive finding of synovitis and bone erosion than non-RA patients (P<.01) (Fig. 1). If we consider the patients with one or more findings as positive, sensitivity and specificity were 76% and 69%, respectively. The FIESTA images also demonstrated the synovitis and bone erosion clearly in more than half of early RA patients. The adjacent structures of the synovium and the endosteal structures, such as the joint fluid and the bone trabeculae, were clearly delineated with the FIESTA images (Fig. 2).

3.2. Postcontrast MRI findings

Table 2 shows the fat-suppressed postcontrast T1-weighted MR findings for differentiation between early RA and non-RA. Synovitis was detected with postcontrast MRI in all 21 RA patients (100%) at the initial stage (Fig. 3). If we consider the patients with one or more findings as positive, sensitivity and specificity were 100% and 69%, respectively. Bilateral synovitis was found in 18 (86%) of these 21 RA patients. The final diagnoses in the five false-positive cases were Sjögren syndrome (n=2), osteoarthritis (n=1), RS3PE syndrome (n=1), and polymyalgia rheumatica (n=1). The detection rate of tenosynovitis in early RA patients was 62% (13/21) and was significantly higher than that of non-RA patients (P<.01).

4. Discussion

Several studies have shown that MRI has enabled clinicians to visually detect bone erosion and active synovitis before the changes are visible on conventional radiographs [8–10]. MRI has been increasingly recognized as a useful method for diagnosis and monitoring of therapeutic response in patients with RA [11–13]. Duer-Jensen et al. [14] reported that MRI evidence of bone edema in the metatarsophalangeal and wrist joints is an independent predictor of future RA in patients with early undifferentiated arthritis, but they did not cover synovitis which is an essential pathologic abnormality in RA. In addition, the RA predictive value of 3-T MRI in undifferentiated arthritis patients has not been reported. There are also good results with regard to the sensitivity and specificity of ultrasound (US), but when the early diagnosis of RA is based on US characterization of intra-articular thickening, this can represent a challenge because intra-articular thickening can be caused not only by synovitis but also by accumulating fluid [15].

Preliminary data showed promising visualization of hand structure at 3-T MRI. Saupe et al. [5] reported that the contrast-to-noise ratios between muscle and bone and between bone and cartilage were significantly higher and that the visibility of the triangular fibrocartilage complex and intercarpal ligaments and cartilage was significantly better on 3-T MR images than on 1.5-T MR images. In our study, higher SNR with 3-T MRI allowed high-resolution MRI depicting the entire structure of the bilateral hands at a time in contrast to a previous study with 1.5-T MRI [8]. In addition, the conspicuity of contrast enhancement is likely to be increased compared with 1.5 T as a consequence of the relatively stronger shortening of increased T1 relaxation times by gadolinium [16].

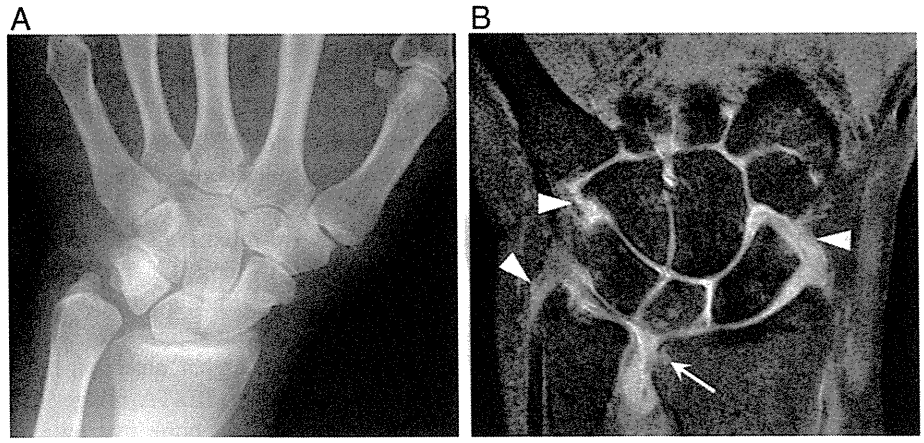

Fig. 1. Early rheumatoid arthritis in a 68-year-old woman. Posteroanterior radiograph of the left hand (A) shows no evidence of rheumatoid arthritis. Fat-suppressed intermediate-weighted FSE image (B) shows a diffuse thickening of the synovium (arrowheads) and a bone erosion (arrow).

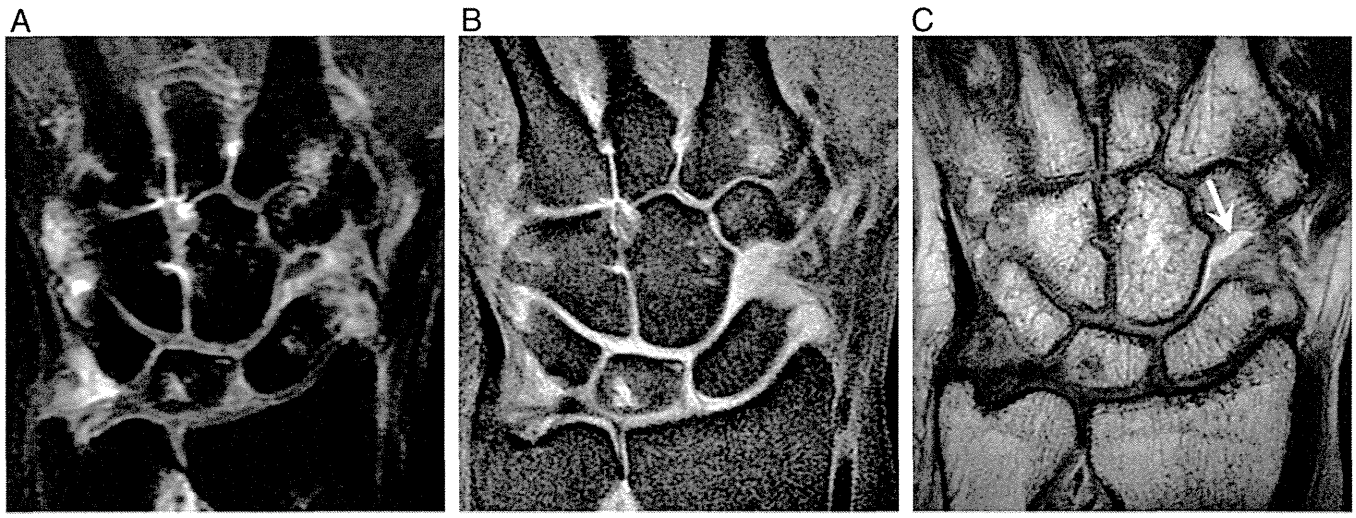

Fig. 2. Early rheumatoid arthritis in a 64-year-old woman. Fat-suppressed gadolinium-enhanced T1-weighted image of the left wrist (A) shows marked periarticular enhancement and bone erosions of carpal bones. Fat-suppressed intermediate-weighted FSE image (B) also depicts the inflamed synovium and bone erosions. In addition, fast imaging employing steady-state acquisition (FIESTA) image (C) delineates a joint fluid (arrow).

The results of this prospective study showed the high performance of postcontrast MRI at 3 T. The most important finding of our study was that synovitis was detected by postcontrast MRI in all 21 early RA patients who did not fulfill the ACR diagnostic criteria at the MR examination (sensitivity=100%). Although we did not perform a comparative study between 1.5-T MRI and 3-T MRI, the results of this study indicated that, with the 3-T MRI, the sensitivity in extracting early RA patients from undifferentiated arthritis was increased to a level that was higher than that reported for 1.5 T imaging [17]. An improved detection would be of interest as it would allow them access to earlier therapeutic measures and improved joint protection while preventing or postponing articular destruction. Furthermore, 3-T MRI may be used to plan aggressive therapy in patients who are suspected of having early-stage RA.

In spite of high sensitivity, the diagnostic specificity of postcontrast MRI at 3 T was still not high (69%). This may be due to the inclusion of populations with other rheumatic disease with similar joint manifestations (e.g., Sjögren syndrome, RS3PE syndrome, and polymyalgia rheumatica). Boutry et al. [18] found that MR findings including synovitis and bone lesions in hands were not different between the RA group and the Sjögren syndrome group. Synovitis of the hands on MRI was also often observed in RS3PE syndrome and polymyalgia rheumatica patients [19,20]. The similar characteristics of MRI findings in polymyalgia rheumatica and RS3PE seem to indicate that the involvement of extra-articular synovial structures represent the common anatomical target of the inflammatory process in these two conditions. Although Marzo-Ortega et al. [20] documented that extracapsular enhancement was higher in the polymyalgia rheumatica group than in the RA group, they found the extracapsular enhancement in half of the RA patients. These rheumatic diseases with similar joint manifestations must be considered in the everyday clinical management of early RA; however, it may be impossible to differentiate patients with early RA from those with these diseases by means of MRI.

Table 2
Fat-suppressed postcontrast T1-weighted MR findings for differentiation between early RA and non-RA

MR Findings	Early RA (n=21)	Non-RA (n=16)	P value
Synovitis	21 (100%)	5 (31%)	<.01
Ipsilateral wrist	2 (10%)	2 (13%)	>.99
Ipsilateral MCP/PIP	1 (5%)	0 (0%)	>.99
Bilateral	18 (86%)	3 (19%)	<.01
Tenosynovitis	13 (62%)	2 (13%)	<.01
Ipsilateral	4 (19%)	2 (13%)	>.99
Bilateral	9 (43%)	0 (0%)	<.01

PIP = Proximal interphalangeal; MCP = metacarpophalangeal joints.

A combination of factors, including altered kidney function, inflammatory burden, and exposure to gadolinium-based contrast agents, plays a role in the development of nephrogenic systemic fibrosis [21]. In a small subset of patients, however, especially those with renal insufficiency and those with severe allergic reactions, use of gadolinium contrast material is contraindicated. Alternative imaging should be considered in patients with these factors. The visualization rates of synovitis and bone erosion in early RA patients were more than half and were significantly higher than those in non-RA patients using unenhanced fat-suppressed intermediate-weighted FSE and FIESTA sequences. The fat-suppressed intermediate-weighted FSE image showed higher detection rate of synovitis and bone erosion than the FIESTA image. In addition, this image is better for viewing bone marrow edema than the FIESTA image due to fat suppression. However, the FIESTA image clearly delineated joint fluid and bone trabeculae and the

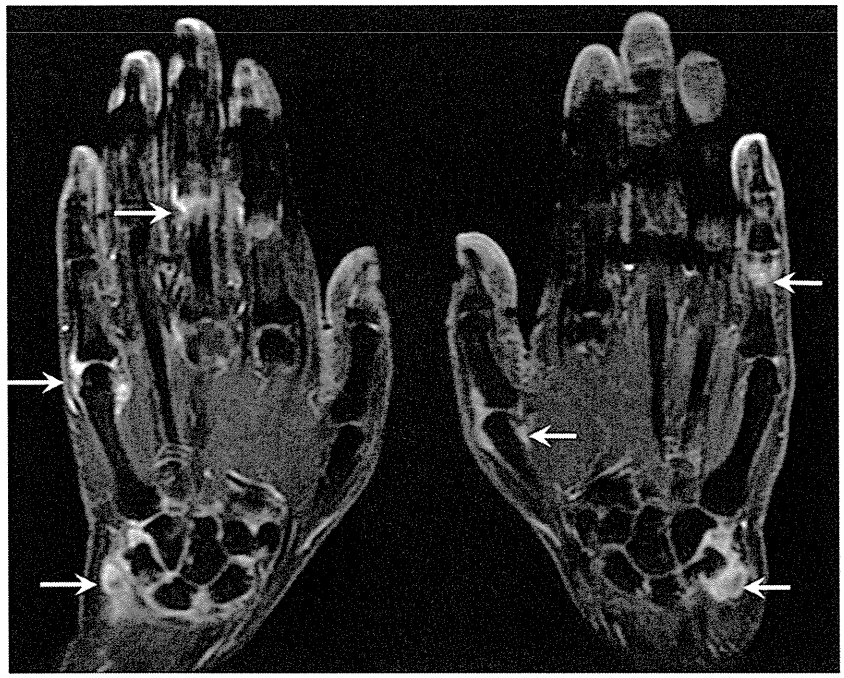

Fig. 3. Early rheumatoid arthritis in a 52-year-old woman. Fat-suppressed gadolinium-enhanced T1-weighted images show marked periarticular enhancement in bilateral wrist joints and in multiple proximal interphalangeal and metacarpophalangeal joints (arrows).

scan time is less than half in comparison with fat-suppressed intermediate-weighted FSE image. These two unenhanced MR images at 3 T are beneficial complementary imaging techniques in early RA patients and should be incorporated into an examination of patients with suspected early RA and contraindications to administration of gadolinium.

Our study had several limitations. First, we performed MRI of the hands only, although RA is a systemic disease. Because the joints of the hands generally are the earliest and most often affected site in early RA patients [22], we considered it feasible to examine only the hands with MRI. Second, the actual added value of 3 T compared with 1.5 T was not directly assessed because the patients underwent only 3-T MRI. It is our impression, however, that the MR image quality at 3 T imaging is noticeably greater than that at 1.5 T imaging. Third, this study included a rather small number of patients. Additional prospective longitudinal study with a larger number of cases may be necessary to confirm the clinical usefulness of 3 T imaging. Fourth, follow-up periods were relatively short. Four of 5 false-positive cases were diagnosed as Sjögren syndrome (n=2), RS3PE syndrome, and polymyalgia rheumatica. It is important that these diseases often overlap with RA. If these patients had fulfilled the ACR diagnostic criteria after further follow-up, the specificity of 3-T MRI might have improved.

In conclusion, MRI at 3 T is a potentially powerful tool for discriminating and managing early-stage RA patients. Because unenhanced sequences had relatively high diagnostic performance, 3-T MRI seems also useful for patients with contraindications to administration of gadolinium.

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