Incident fractures

Incident fractures were determined in 3231 vertebrae in 279 cases by consensus reading on semiquantitative assessment, and they were observed in 42 vertebrae (1.3%) in 29 cases (10.4%). The distribution of incident fractures is also shown in Fig. 1. L1 was the most frequent site (19.0%) of incident fractures. The changes in grade on the semiquantitative assessment are shown in Table 3. Thirty-five cases from grade 0, 5 from grade 1, and 2 from grade 2 were upgraded.

The cutoff values of PHr, AHr, and combined PHr and AHr, PAHr, determined employing sensitivity and specificity in incident fractures, are shown in Table 4. The cutoff values of 15% and 20% in PHr were 50.83% and 36.67% for sensitivity, and 99.90% and 99.93% for specificity, respectively. The cutoff values of 3mm and 4mm in AHr were 65.00% and 51.67% for sensitivity, and 99.77% and 99.92% for specificity, respectively. The cutoff values of 15% and 3mm and 15% and 4mm in PAHr, combined PHr and AHr, were 50.83% and 49.17% for sensitivity, and 99.90% and 99.92% for specificity, respectively. When the cutoff values for PAHr were 15% and 3mm, and 15% and 4mm, the frequencies of incident fractures, on a per case or per vertebra basis, were 27 (9.7%) per case and 43 (1.2%) per vertebra, and 26 (9.3%) per case and 41 (1.2%) per vertebra, respectively. These cutoff values of PAHr were better for sensitivity than those of 20% and 3mm (36.67%) and 20% and 4mm (36.67%), but these specificities were almost the same (99.93% and 99.94%).

Table 2. Values of Ha/Hp, Hm/Hp, and Hm/Ha ratios from T4 to L5 in grade 0 at the baseline

Level	*n*	Ha/Hp	Hm/Hp	Hm/Ha
T4	215	0.92 ± 0.05	0.92 ± 0.04	1.00 ± 0.04
T5	240	0.91 ± 0.05	0.92 ± 0.04	1.01 ± 0.04
T6	255	0.89 ± 0.05	0.91 ± 0.04	1.03 ± 0.05
T7	246	0.89 ± 0.05	0.91 ± 0.03	1.03 ± 0.05
T8	255	0.90 ± 0.06	0.91 ± 0.04	1.01 ± 0.05
T9	253	0.94 ± 0.05	0.93 ± 0.04	0.99 ± 0.04
T10	250	0.93 ± 0.06	0.92 ± 0.04	1.00 ± 0.05
T11	231	0.88 ± 0.06	0.89 ± 0.04	1.02 ± 0.05
T12	219	0.87 ± 0.05	0.89 ± 0.04	1.02 ± 0.04
L1	242	0.89 ± 0.06	0.89 ± 0.04	1.01 ± 0.05
L2	256	0.93 ± 0.06	0.91 ± 0.04	0.98 ± 0.05
L3	260	0.98 ± 0.07	0.95 ± 0.04	0.97 ± 0.05
L4	259	1.02 ± 0.09	1.01 ± 0.06	1.00 ± 0.06
L5	167	1.12 ± 0.09	1.07 ± 0.06	0.96 ± 0.06
Totals	3348	0.93 ± 0.08	0.93 ± 0.06	1.00 ± 0.05

Values are mean ± SD

Discussion

Morphological changes such as endplate deformity, buckling of the cortex, lack of parallelism of the endplate, and loss of vertebral continuity [17] are characteristics of vertebral fractures. These findings can be recognized easily by semiquantitative assessment, but they might be missed by other quantitative methods. However, associations with degenerative osteosclerotic changes and scoliosis are often difficult to determine in the diagnosis of incident fractures.

It is important to distinguish false positives based on radiographic problems, e.g., incorrect projection of the X-ray, from real incident vertebral fractures. When morphometric criteria are used to define incident fractures, it is essential to maintain good quality control and assurance in the radiographic procedure.

Table 3. Changes of grade in incident fracture on semiquantitative assessment

Incident fracture	Grade			Number	
	Baseline		Follow-up	Vertebrae	Cases
(−)	0	→	0	3384	
	1	→	1	122	
	2	→	2	61	
	3	→	3	17	
Totals				3584	250
(+)	0	→	1	23	
	0	→	2	7	
	0	→	3	5	
	1	→	2	4	
	1	→	3	1	
	2	→	3	2	
				42	29
Totals				3626	279

Table 4. Cutoff values of percent height ratio (PHr), absolute height reduction (AHr), and combined PHr and AHr (PAHr), and sensitivity and specificity for incident fracture, and frequencies of incident fracture on per case basis and per vertebra basis

Value	Cutoff	Sensitivity (%)	Specificity (%)	Frequency of incident fractures			
				Per case basis		Per vertebra basis	
				n	%	*n*	%
PHr	≧15%	50.83	99.90	27	9.7	43	1.2
	≧20%	36.67	99.93	22	7.9	35	1.0
AHr	≧3mm	65.00	99.77	35	12.5	54	1.5
	≧4mm	51.67	99.92	28	10.0	43	1.2
PAHr	≧15%, 3mm	50.83	99.90	27	9.7	43	1.2
	≧15%, 4mm	49.17	99.92	26	9.3	41	1.2
	≧20%, 3mm	36.67	99.93	22	7.9	35	1.0
	≧20%, 4mm	36.67	99.94	22	7.9	34	1.0

It is important to define incident fractures, especially in the evaluation of drug therapy and international comparisons of the epidemiology of osteoporosis. In defining incident fractures, many methods, including visual semiquantitative assessment and quantitative morphometry, have been proposed.

In alendronate clinical trials, an incident fracture was defined as a decrease of ≥20% and ≥4mm in the height of any vertebrae, relative to the baseline [2,15]. The effect of risedronate on vertebral incident fractures was evaluated by both quantitative and semiquantitative assessments [12,18]. An incident fracture was defined as ≥15% reduction at anterior, middle, or posterior heights of the vertebral body for quantitative assessment [19], and an increase of one or more grade for semiquantitative assessment [3], compared with baseline thoracic and lumbar radiographs.

In raloxifen clinical trials, the criterion for diagnosis of an incident vertebral fracture was based on a reduction in the anterior, middle, and/or posterior vertebral height of ≥20% and at least 4mm, compared with the baseline radiograph [20,21], as well as a grade change of at least one for semiquantitative assessment [21]. In a parathyroid hormone [(1–34)PTH] clinical trial, an incident vertebral fracture was assessed by the grade of deformity, a decrease in height of approximately more than 20%, whereas worsening of the preexisting deformity was not analyzed [22].

Although vertebral fractures associated with osteoporosis are frequently observed, the criteria for incident vertebral fractures have not yet been defined in Japan. In the present study, the cutoff values of vertebral height reduction and ratio in Japanese women were evaluated using morphometry, and semiquantitative assessment as the gold standard.

The morphometry of vertebral heights at the anterior, middle, and posterior of vertebral bodies from T4 to L4 showed excellent reproducibilities (RMS = 1.10%–1.70%). However, in the diagnosis of incident vertebral deformities, semiquantitative assessments by trained radiologists might be better than morphometric techniques [23]. In addition, a comparative study of semiquantitative and morphometric methods has shown similar results for the assessment of vertebral fractures in osteoporosis [24]. For these reasons, we adopted a semiquantitative assessment as the gold standard.

Several methods for defining incident vertebral fractures, including the spinal deformity index and point prevalence [25,26], have been reported [27]. The percentage change in anterior, middle, and posterior vertebral heights, and/or absolute vertebral height reductions, are used as criteria [28]. Recently, among these methods the relative vertebral height ratio and/or absolute height reduction have been mainly used. Regarding the height ratio, 15% and 20% reductions have been often used to define deformity, but there is no information on which criterion is better. In the present study, in Japanese women, a cutoff value of 15% reduction of vertebral height was better than that of 20%, because the 15% reduction had better sensitivity (50.83% vs 36.67%), and almost the same specificity (99.90% vs 99.93%).

In clinical trials for osteoporosis treatment, it is necessary to consider two points in the assessment of incident vertebral fractures; incident fractures are rare events, but stringent morphometric criteria can also lead to failure to detect incident fractures observed on radiograms. Therefore, to reduce false positives or false negatives, it is essential to establish cutoff levels for the relative ratio and absolute reduction of vertebral heights that can satisfy the requirements for both good sensitivity and specificity.

In the present study, we selected, as relative ratios and absolute reduction of vertebral heights, 15% and 3mm, and 15% and 4mm, respectively. The sensitivity

and specificity of these criteria were 50.83% and 49.17%, and 99.90% and 99.92%, respectively.

Using quantitative morphometry and the semiquantitative approach with 350 Caucasian and Asian postmenopausal women with one to seven prevalent vertebral fractures and a T score of no more than 2 SD of lumbar BMD, the cutoff values of PAHr were ≥15% and 3mm, and 20% and 4mm for the relative ratio and absolute vertebral height reduction. The sensitivity and specificity rates for incident fractures were 75.44% and 47.37%, and 98.75% and 99.84%, respectively [17]. Compared with the results of our present study, the sensitivity rate for incident fractures differed, whereas the specificity rate was almost the same. The difference in the sensitivity rate might be related to differences in the subjects or different criteria for participation in the study.

We adopted as defining criteria for incident fractures both an absolute vertebral height reduction ≥3mm or ≥4mm and a relative height ratio ≥15%. The adaptation of these two cutoff criteria can decrease the possibility of artifacts that might occur in baseline and follow-up radiography.

Vertebral heights and ratios differ between races, e.g., Caucasian and Japanese women. The mean Japanese vertebral heights were 1–2mm shorter than those for Caucasians [29], reflecting the possibility that the Japanese are of a shorter stature. However, it has been reported that the prevalence of vertebral fractures was similar among Hong Kong Chinese and American Caucasians when population-specific means and SD were used for defining vertebral fractures [30].

In conclusion, the morphometric criteria, both a relative height ratio ≥15% and an absolute height reduction ≥3mm or ≥4mm of incident fracture combined with a semiquantitative assessment were determined, and these measures will provide useful information in the study of clinical osteoporosis, especially for international comparisons.

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Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study

Kazuhiro Kushida[1], Masataka Shiraki[2], Toshitaka Nakamura[3], Hideaki Kishimoto[4], Hirotoshi Morii[5], Kichizo Yamamoto[6], Kiyoshi Kaneda[7], Masao Fukunaga[8], Tetsuro Inoue[9], Mitsuyoshi Nakashima[10], and Hajime Orimo[11]

[1]Department of Orthopedic Surgery, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan
[2]Research Institute and Practice for Involutional Diseases, Nagano, Japan
[3]University of Occupational and Environmental Health, Fukuoka, Japan
[4]Sanin Rosai Hospital, Tottori, Japan
[5]Japan Osteoporosis Society, Osaka, Japan
[6]Hakuai Hospital, Tottori, Japan
[7]Bibai Rosai Hospital, Hokkaido, Japan
[8]Kawasaki Medical School, Okayama, Japan
[9]Aoyama General Hospital, Aichi, Japan
[10]Hamamatsu Institute of Clinical Pharmacology and Therapeutics, Hamamatsu, Japan
[11]Tokyo Metropolitan Geriatric Medical Center, Tokyo, Japan

Abstract The risk-reducing effect of alendronate on vertebral fractures has been consistently reported. In a 2-year, randomized, double-blind, active drug-controlled (1μg alfacalcidol) double-dummy study, we also reported that alendronate (5.0mg) had a fracture-reducing effect in Japanese patients with preexisting vertebral fractures. The present report describes the risk-reducing effect of alendronate (5.0mg) for 3 years in postmenopausal osteoporotic patients. The 3-year treatment period consisted of the original 2-year double-blind study followed by a 1-year extension. A total of 170 postmenopausal female patients were involved in the third year; 90 received alendronate and 80 received alfacalcidol. Both efficacy and safety were analyzed in these 170 patients. Vertebral fracture was determined by quantitative morphometry, and vertebral bone mineral density (BMD) was measured by the DXA method (dual-energy X-ray absorptiometry). The primary efficacy endpoint was the incidence of vertebral fracture, excluding fracture cases that occurred in the first 6 months after treatment initiation. The cumulative incidence of vertebral fracture at 3 years was 7.8% (7/90) in the alendronate group and 18.8% (15/80) in the alfacalcidol group, indicating a significantly reduced risk of fractures in the alendronate group (relative risk = 0.41, 95% CI = 0.18–0.97). Lumbar spine BMD increased by 9.2% in the alendronate group (n = 26) and by 1.4% in the alfacalcidol group (n = 22) at 3 years. The safety profile of alendronate during 3 years of treatment was similar to that of alfacalcidol. The present study thus demonstrated that treatment with alendronate 5.0mg for 3 years increased vertebral BMD and reduced the risk of vertebral fractures in Japanese, postmenopausal women with osteoporosis.

Offprint requests to: K. Kushida
(e-mail: kkushida@tm.hama-med.ac.jp)
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Introduction

Osteoporosis is a common disorder in the elderly population and is associated with increased risk of bone fractures and spinal deformity. The prevention and treatment of osteoporosis have been challenging issues for the medical community in Japan, which is a rapidly aging society. In 1997, approximately 92000 cases of hip fracture occurred in Japan, and about 80% of these patients were women [1]. The lifetime risk of vertebral fracture was estimated to be 37% or greater in women over 50 years old [2]. Low bone mineral density (BMD) is associated with increased fracture risk, and pharmacological therapy is directed at reducing fracture risk by increasing BMD.

Alendronate (ALN) exerts a potent inhibitory effect on bone resorption [3,4]. In European and American studies, ALN at a dose of 10mg/day has consistently been shown to increase BMD at the spine, hip, and other skeletal sites and to reduce the risk of all types of fractures [5–12]. In long-term extensions of the original phase III studies, BMD continued to increase at the spine during ALN treatment for at least 7 years; ALN was generally well tolerated and had an adverse experience profile similar to that of placebo [13,14].

In Japan, we conducted a 2-year, double-blind comparative study and found that ALN 5mg significantly lowered the incidence of one or more vertebral fractures to a greater extent than did alfacalcidol after 6

months or more of treatment [15]. In the same study, ALN also significantly reduced the incidence of multiple vertebral fractures compared with alfacalcidol during 2 years of treatment [15].

Bisphosphonates with increase in lumbar spine BMD in Japanese patient with osteoporosis have been widely studied, but preparations with a risk-reducing effect on vertebral fracture in Japanese patients with osteoporosis for 3 years have apparently not been reported. We herein describe the safety and efficacy of ALN in reducing the incidence of vertebral fractures during a total study period of 3 years, which consisted of the original 2-year double-blind study plus a 1-year extension.

Patients and methods

Study design

The study was first conducted as a 2-year, double-blind, comparative trial and then was extended for another year. The study was performed at 57 departments of 55 institutional centers in Japan nationwide. Patients were randomized to receive either ALN (5 mg; Merck, Whitehouse Station, NJ, USA, and Banyu Pharmaceutical, Tokyo, Japan) or alfacalcidol (1 μg; Teijin, Tokyo, Japan) once daily in a double-blind fashion.

The study extension was approved in advance by the institutional review boards (IRB) of the individual participating institutional sites. The subjects enrolled in the preceding 2-year double-blind study who completed the study and were judged eligible for the extended doses were advised of the objectives and procedures of the extension study. Informed written consent was then reobtained from these patients. The present study, including the 1-year extension, was conducted from September 1998 through November 2001 in accordance with the spirit of the Declaration of Helsinki and the Guideline for Good Clinical Practice (Ministry of Health, Labour and Welfare of Japan, Notification No. Yakuhatsu 874, dated October 2, 1989).

Every patient enrolled in the 1-year extension study was given the same study drugs as administered in the preceding 2-year, double-blind, comparative study. The following study drugs were administered: one tablet of ALN 5 mg plus one tablet of alfacalcidol placebo in the ALN group and one tablet of alfacalcidol 1 μg plus one tablet of ALN placebo in the alfacalcidol group. All study drugs were taken once daily on arising with approximately 180 ml water. The patients were instructed to remain upright and refrain from any food, beverage, or other drug intake for at least 30 min after drug ingestion. Calcium lactate powder (1.5 g) was taken once daily after the evening meal.

Subject population

Of 242 patients who completed the preceding 2-year double-blind study, 179 participated in this 1-year extension. Nine patients ($n = 3$ in the ALN group and $n = 6$ in the alfacalcidol group) were excluded from the current analysis, leaving 170 postmenopausal female patients ($n = 90$ in the ALN group and $n = 80$ in the alfacalcidol group) for analysis. As defined in the patient criteria, the female patients were 65 years old or older, ambulatory, and had one to four preexisting vertebral fractures associated with osteoporosis at the start of the preceding double-blind study.

Patients were excluded if they had ever been treated with a bisphosphonate or had been treated with any of the following within 8 weeks of the start of the study: pharmacologically active vitamin D preparations (including alfacalcidol), anabolic steroid, calcitonin, ipriflavone, vitamin K, male sex hormone (androgen), female sex hormone (estrogen), antiestrogen, or calcium preparations. Other exclusion criteria included metabolic bone diseases (e.g., hyperthyroidism, osteomalacia, renal osteodystrophy), diabetes, history of peptic ulcer, reflux esophagitis, rheumatoid arthritis, history of malignancy, serious liver or heart disease, renal dysfunction, or serum creatinine concentration ≥ 1.5 mg/dl at the start of the preceding double-blind study. Table 1 presents the baseline characteristics at the start of the original 2-year double-blind study for the female patients enrolled in this 1-year extension.

Evaluation of vertebral fractures

Vertebral fractures were evaluated using radiographs of thoracic (T8 centered) and lumbar vertebrae (L3 centered) that were taken from the anterior and lateral sides at baseline and every 6 months during treatment. New vertebral fractures were identified on radiographs by experienced researchers and were confirmed using quantitative morphometry. Three vertebral heights, Ha, Hc, and Hp, were measured, and a new vertebral fracture was defined as a decrease of 20% or more in any of these heights, relative to baseline.

The primary efficacy endpoint was the proportion of patients with a new vertebral fracture more than 6 months after initiating treatment (vertebral fractures that occurred within 6 months after the start of treatment were not considered). The secondary endpoints were (1) the 3-year cumulative incidence of patients who experienced vertebral fractures (excluding those in the first 6 months) and (2) the percentage of patients who developed multiple (more than one) new vertebral fractures.

Table 1. Demographics and baseline characteristics of female patients (n = 170) enrolled in the full 3-year study[a]

Characteristics	Alendronate (n = 90)	Alfacalcidol (n = 80)
Age, years	71.2 (5.3)	72.6 (5.7)
Height, cm	146.5 (6.0)	145.0 (5.9)
Body weight, kg	49.5 (8.5)	48.9 (7.7)
Years since menopause	22.0 (7.2)	22.4 (7.6)
No. of vertebral fractures at baseline[a]		
1	46	35
2	26	26
3	9	10
4	9	9
ALP (IU/l)	211 (82, 93–482)[b]	224 (90, 52–535)[b]

[a] Baseline refers to the beginning of the original 2-year double-blind study
[b] Values are presented as mean (SD), except for ALP, which is given as mean (SD, Min.–Max.)

Measurement of vertebral BMD

BMD of the spine (L2–L4) was measured by dual-energy X-ray absorptiometry (DXA) at baseline and at 12, 24, and 36 months of treatment in a subset of patients (at centers with bone densitometry equipment).

Safety evaluation

The safety of the study drugs was assessed at each examination by evaluating adverse experiences (AEs) and abnormal changes in clinical laboratory test values. The following laboratory tests were performed: hematology: red blood cell count, white blood cell count, differential white blood cells (basophils, eosinophils, neutrophils, lymphocytes, monocytes), hemoglobin, hematocrit, and platelet count; blood chemistry: AST (GOT), ALT (GPT), γ-GTP, alkaline phosphatase (ALP), LDH, CPK, BUN, creatinine, albumin, total bilirubin, total cholesterol, Na, K, Cl, Ca, and P; and urinalysis: protein and sugar.

Statistical analyses

Efficacy was analyzed by intention to treat (ITT) using all randomized patients with at least 12 months of follow-up. The primary efficacy endpoint was the proportion of patients with a new vertebral fracture more than 6 months after initiating treatment (vertebral fractures that occurred within 6 months after the start of treatment were not considered). It was decided before unblinding that the primary analyses would exclude fractures occurring during the first 6 months, because this is the minimum time that is required to refill existing resorption sites and begin to restore bone strength, as predicted by bone remodeling theory. A 95% confidence interval for the mean difference in fracture incidence between the treatment groups was calculated. The time to the first new vertebral fracture was profiled in a survival analysis (estimation of survival function and log-rank test) using the life table method.

BMD was assessed as the percentage change from baseline in mean density (g/cm^2) of the lumbar vertebrae L2–L4 at 12, 24, and 36 months of treatment and was compared between the treatment groups using the two-sample t test procedure after adjusting for multiplicity of data points.

Safety was analyzed using the primary endpoint of clinical symptoms and laboratory abnormalities. The incidences of adverse events and drug-related adverse events were compared between the treatment groups using Fisher's exact test.

The level of significance was 0.05 (two-tailed) for the efficacy analysis (primary and secondary endpoints) and the safety analysis (primary endpoint).

Results

Frequency of vertebral fractures

Baseline characteristics (before initiating treatment) were similar for women who entered the third year in both treatment groups; there were no significant differences (see Table 1). The 3-year cumulative increase in new vertebral fractures was significantly less in the ALN group than in the alfacalcidol group (log-rank test, P = 0.0341; Fig. 1). Overall, 7/90 (7.8%) and 15/80 (18.8%) in the ALN and alfacalcidol groups, respectively, experienced new vertebral fractures (relative risk = 0.42, 95% CI = 0.18–0.97; Fig. 2). The between-treatment difference in the percentage of patients with vertebral fractures was 11% (95%CI = 0.8%–21.2%). Thus, ALN reduced vertebral fracture risk relative to alfacalcidol ($P < 0.05$).

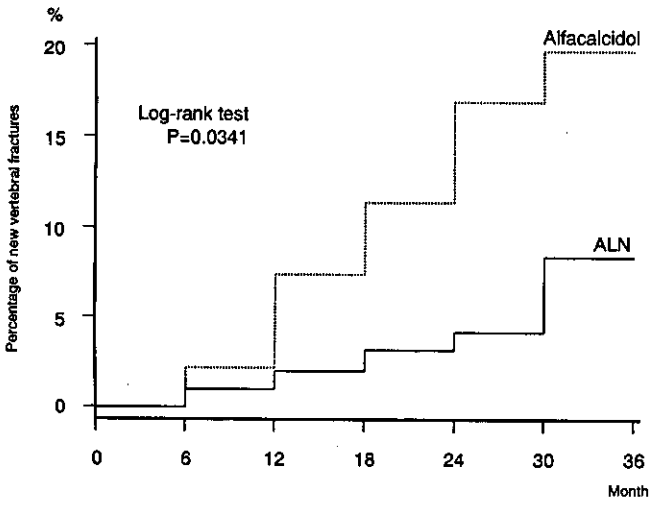

Fig. 1. Cumulative distribution of patients with new vertebral fractures. *ALN*, alendronate

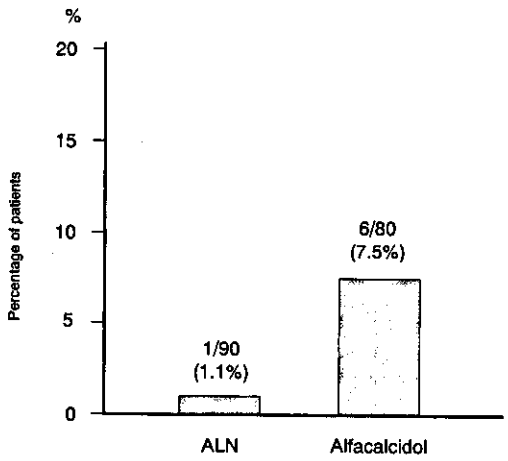

Fig. 3. Percentage of patients with multiple new vertebral fractures: the difference in incidence between groups was 6.4% (95% CI, 0.2%–12.6%)

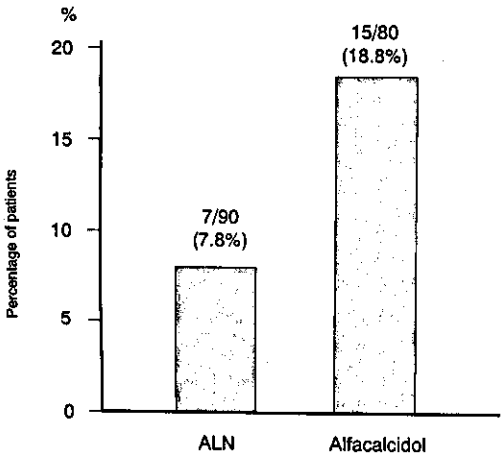

Fig. 2. Percentage of patients with new vertebral fractures: the difference in incidence between groups was 11.0% (95% CI, 0.8%–21.2%)

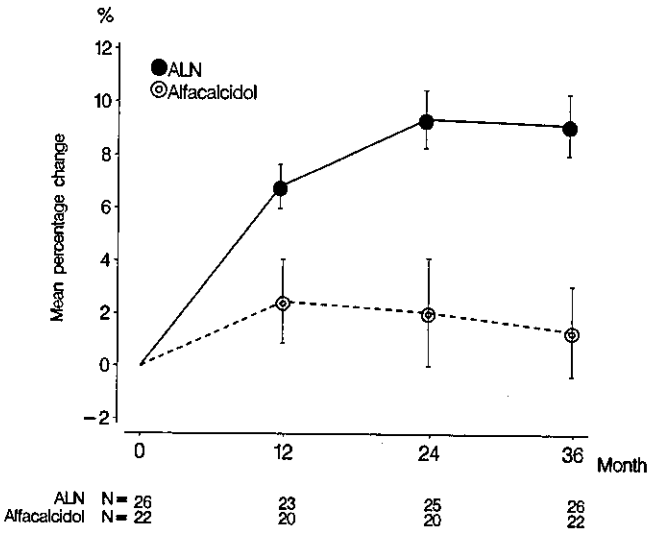

Fig. 4. Percent change profile of L2–L4 BMD (mean ± SE)

Multiple vertebral fractures

The number and percentage of patients who experienced multiple new vertebral fractures were 1/90 (1.1%) and 6/80 (7.5%) in the ALN and alfacalcidol groups, respectively (Fig. 3). The between-treatment difference in the percentage of patients with multiple new vertebral fractures was 6.4% (95% CI = 0.2–12.6, Fig. 3). Thus, ALN significantly reduced the risk of multiple vertebral fractures compared with alfacalcidol ($P < 0.05$).

Lumbar spine BMD

Percent changes from baseline in L2–L4 BMD were calculated at 12, 24, and 36 months in patients who had not developed lumbar spine fractures at any measurement. As shown in Fig. 4, there was a greater increase in lumbar spine BMD in the ALN group than in the alfacalcidol group (9.2% vs 1.4% increase at 3 years of treatment). The increases in spine BMD were significantly greater for ALN compared to alfacalcidol at these three time points (two-sample t test using Bonferroni's multiple comparison method).

Laboratory data

Serum levels of ALP, Ca, and phosphorus were considered parameters of bone metabolism. Serum ALP levels decreased significantly during the first 6 months of ALN treatment and remained consistently decreased for 3

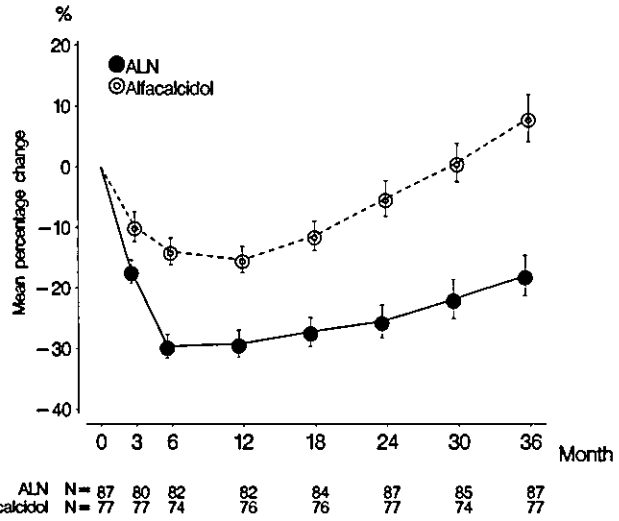

Fig. 5. Percent change profile of serum ALP (mean ± SE)

years. In contrast, alfacalcidol produced only a small decrease in ALP at 6 to 12 months, which gradually returned to baseline levels by month 24. Although serum Ca slightly decreased with ALN and increased with alfacalcidol, the between-group difference was not statistically significant. Serum phosphorus also tended to decrease in the ALN group, but no statistically significant difference was observed between the treatment groups.

Safety

No statistically significant difference in the incidence of drug-related AEs was observed between the ALN and alfacalcidol groups (22.2% vs 16.3% for subjective symptoms/objective symptoms and 12.2% vs 15.0% for laboratory abnormal findings). Similarly, the incidence of gastrointestinal AEs did not differ significantly between the treatment groups (ALN 14.4% vs alfacalcidol 13.8%). The drug-related gastrointestinal AEs occurring in 2% or more of patients (i.e., two events or more in either treatment group) were constipation (3.3%, three events), stomach heaviness (2.2%, two events), stomach discomfort (2.2%, two events), and gastritis (5.6%, five events) in the ALN group, and constipation (3.8%, three events), abdominal pain (2.5%, two events), stomach discomfort (2.5%, two events), and gastritis (3.8%, three events) in the alfacalcidol group.

Discussion

In this study, postmenopausal Japanese women with osteoporosis manifested as preexisting vertebral fractures were treated with ALN (5 mg/day) or alfacalcidol (1 μg/day) for 3 years. The results demonstrated that the incidence of vertebral fractures after 6 months was significantly lowered by ALN compared with alfacalcidol. The increases in spine BMD were significantly greater for ALN compared to alfacalcidol ($P < 0.001$), and the BMD-elevating effect of ALN lasted continuously throughout the 3-year period. Furthermore, serum ALP levels for ALN treatment group showed significant decrease compared to alfacalcidol group beyond month 6 ($P < 0.001$), and this decrease was rather persistent for 3 years, suggesting a long-lasting inhibitory action of the drug on the bone metabolism.

Upon absorption, bisphosphonates are rapidly localized to active sites of bone remodeling, where they exhibit their pharmacological actions on osteoclasts. Although the precise pharmacological mechanism of action of ALN remains elusive, it is known that nitrogen-containing bisphosphonates, including ALN, block the mevalonic acid pathway, thereby inhibiting the prenylation of G protein(s), which play a key role in intracellular signal transduction. As a result, the bone-resorbing activity of osteoclasts is suppressed [16–18]. It is believed that the four-carbon amino side chain of ALN enables the drug to suppress osteoclastic bone resorption without interfering with bone calcification [19], thus normalizing bone metabolism [20]. This conclusion is supported by data from animal studies showing that ALN increases bone strength along with BMD [21,22]. Moreover, histological investigation of iliac bone biopsies revealed normal bone calcification in patients treated with ALN over 3 years [23]. Furthermore, bone specimens from postmenopausal women with osteoporosis treated with ALN for 2–3 years showed that the mean degree of mineralization was restored to normal levels [24,25].

In clinical studies conducted in Western countries, ALN (5–10 mg/day) significantly reduced the incidence of both vertebral and nonvertebral fractures by about half, which was associated with increased BMD and decreased bone resorption markers [5–13].

Clinical studies have also been conducted in Japan to assess the efficacy and safety of alendronate. Of relevance to the current study, a double-blind, alfacalcidol-controlled study showed that ALN 5 mg resulted in an increase of 6% or more in lumbar spine BMD at 48 weeks compared with an increase of approximately 1% with alfacalcidol [26–29]. In an earlier report from the current alfacalcidol-controlled study, treatment with ALN 5 mg/day for 2 years significantly reduced vertebral fracture risk in Japanese osteoporotic patients; this risk reduction was similar to that observed in studies conducted outside Japan with ALN 5–10 mg/day [15]. In addition, ALN was generally well tolerated

during 2 years of treatment, and the safety profile of ALN was similar to that of alfacalcidol [15].

The safety analysis in the present study revealed no statistically significant differences in the incidence of drug-related AEs between the ALN and alfacalcidol groups. The incidences of drug-related AEs observed in this study were similar to those reported in the preceding 2-year comparative study [15]. Moreover, the incidences of gastrointestinal AEs did not differ significantly between the treatment groups.

Esophageal ulcer resulting from mucosal irritation has occasionally been described with the use of bisphosphonates [30–32]. In the present study, however, no severe cases of esophageal ulcer were observed during the 1-year extension or the preceding 2-year double-blind study. Previous placebo-controlled studies have demonstrated that ALN was well tolerated, with an incidence of AEs similar to that of placebo [13,32]. In the Fracture Intervention Trial (FIT), the incidences of gastroduodenal perforation, ulcer, and/or bleeding were similar in the ALN and placebo groups [10]. Other studies have demonstrated that the occurrence of gastrointestinal disorders, including esophagitis, may be markedly reduced when the recommended dosing instructions are adhered to [32–34].

In conclusion, treatment with ALN 5 mg/day for 3 years significantly reduced the risk of vertebral fractures and was generally well tolerated in postmenopausal Japanese women with osteoporosis.

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Association of a single-nucleotide polymorphism in low-density lipoprotein receptor-related protein 5 gene with bone mineral density

Tomohiko Urano[1], Masataka Shiraki[2], Yoichi Ezura[3], Masayo Fujita[1], Emiko Sekine[1], Shinjiro Hoshino[1], Takayuki Hosoi[4], Hajime Orimo[5], Mitsuru Emi[3], Yasuyoshi Ouchi[1], and Satoshi Inoue[1,6]

[1]Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[2]Research Institute and Practice for Involutional Diseases, Nagano, Japan
[3]Department of Molecular Biology, Institute of Gerontology, Nippon Medical School, Kawasaki, Japan
[4]Tokyo Metropolitan Geriatric Medical Center, Tokyo, Japan
[5]Health Science University, Yamanashi, Japan
[6]Research Center for Genomic Medicine, Saitama Medical School, Saitama, Japan

Abstract Low-density lipoprotein receptor-related protein 5 (LRP5) is an important regulator of osteoblast growth and differentiation, affecting peak bone mass in vertebrates. Here, we analyzed whether the *LRP5* gene was involved in the etiology of postmenopausal osteoporosis, using association analysis between bone mineral density (BMD) and an *LRP5* gene single-nucleotide polymorphism (SNP). Association of an SNP in the *LRP5* gene at IVS17-1677C > A (intron 17) with BMD was examined in 308 postmenopausal Japanese women (65.2 ± 9.6 years; mean ± SD). The subjects bearing at least one variant A allele (CA + AA; n = 142) had significantly lower Z scores for total body and lumbar BMD than the subjects with no A allele (CC; n = 166) (total body, 0.08 ± 1.09 versus 0.50 ± 1.03; P = 0.0022; lumbar spine, −0.42 ± 1.43 versus −0.02 ± 1.42; P = 0.013). These findings suggest that the *LRP5* gene is a candidate for the genetic determinants of BMD in postmenopausal women, and this SNP could be useful as a genetic marker for predicting the risk of osteoporosis.

Key words wnt · LRP5 · osteoporosis · bone mineral density · polymorphism

Introduction

Osteoporotic fracture is a serious event in an increasingly aging population. Low bone mass is one of the most significant risk factors. Twin and sibling studies have revealed that the proportion of variance of bone mineral density (BMD) accounted for by genetic factors is around 50%–90% [1–6]. These studies have suggested that the variation in BMD among individuals is largely caused by genetic factors. Therefore, genetic markers that are correlated with BMD would be useful for predicting future bone loss and for clarifying the mechanism of bone loss in osteoporosis. After an association of BMD with vitamin D receptor (VDR) genotypes was reported [7], polymorphisms in several other genes were investigated [8]. These genes included those implicated in bone formation by the regulation of osteoblast growth and differentiation, such as transforming growth factor beta 1 (TGFβ1) [9], collagen type Ia1 (COLIA1) [10], parathyroid hormone (PTH) [11], and p57Kip2 (CDKN1C) [12]. Considering the polygenetic nature of BMD distribution and the multiplicity of endocrine factors known to regulate bone mass and bone turnover, it is important that the panel of candidate genes could be expanded to elucidate the whole genetic background of osteoporosis.

The Wnt signaling pathway plays a pivotal role in embryonic development and oncogenesis [13,14]. Studies using *Drosophila*, *Xenopus*, and mammalian cells have established a canonical signaling pathway [15–17]. Both genetic and biochemical results have provided solid evidence indicating that FZ proteins function as Wnt receptors. Wnt proteins bind Frizzled (FZ) and prevent glycogen synthase kinase 3 (GSK3)-dependent phosphonylation of β-catenin, leading to the stabilization of β-catenin. Meanwhile, the low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and LRP6) were found to be also required for the Wnt signaling pathway as Wnt co-receptors [18,19]. Recent reports have demonstrated that the Wnt-β-catenin signaling pathway regulates bone density through LRP5 [20–23]. Inactivating mutations in LRP5 decrease bone mass and cause the autosomal-recessive disorder osteoporosis-pseudoglioma syndrome in humans [20] and mice [21]. Conversely, activating mutations in LRP5 are linked to autosomal-dominant high-bone mass traits [22,23]. These data suggest that LRP5, which modulates

Offprint requests to: S. Inoue
(e-mail: inoue-ger@h.u-tokyo.ac.jp)
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Wnt signaling, controls bone metabolism in vivo in mammals. To examine the possible contribution of the *LRP5* gene to the etiology of involutional osteoporosis, we investigated an association between polymorphism in this gene and BMD in Japanese women.

Subjects and methods

Subjects

Genotypes were analyzed in DNA samples obtained from 308 healthy postmenopausal Japanese women (mean age ± SD; 65.2 ± 9.6 years) living in Nagano prefecture, Japan. Exclusion criteria included endocrine disorders such as hyperthyroidism, hyperparathyroidism, diabetes mellitus, liver disease, renal disease, use of medications known to affect bone metabolism (e.g., corticosteroids, anticonvulsants, heparin), or unusual gynecologic history. All women were non-related volunteers and provided informed consent before this study.

Measurement of BMD and biochemical markers

The lumbar spine BMD and total body BMD (in g/cm^2) of each participant were measured by dual-energy X-ray absorptiometry, using fast-scan mode (DPX-L; Lunar, Madison, WI, USA). We measured serum concentrations of calcium (Ca), phosphate (P), alkaline phosphatase (ALP), intact osteocalcin (I-OC; enzyme-linked immunosorbent assay [ELISA]; Teijin, Tokyo, Japan), intact parathyroid hormone (PTH), calcitonin, 1, 25$(OH)_2D_3$, total cholesterol (TC), and triglyceride (TG). We also measured urinary pyridinoline (PD; HPLC method) and deoxypyridinoline (DPD; HPLC method). The BMD data were recorded as "Z scores"; that is, deviation from the weight-adjusted average BMD for each age. The Z scores were calculated using installed software (Lunar DPX-L) on the basis of data from 20000 Japanese women.

SNP Selection

A polymorphic variation of the *LRP5* gene was extracted from the JSNP-database (http://snp.ims.u-tokyo.ac.jp/index.html), and was denoted as IVS17-1677C > A according to its localization on the gene.

Genotyping procedure

Genotypes of IVS17-1677C > A were determined using the SNP-dependent (Sd)-polymerase chain reaction (PCR) method, a modified allele-specific PCR of polymorphic sequence as previously described [24,25]. Two allele-specific primers (AS-primers) and one reverse primer were prepared per single-nucleotide polymorphism (SNP). The AS-primers (long and short) have a five-base difference between them; each has a polymorphic nucleotide of the SNP sequence at the 3′ ends, and an additional artificial mismatch introduced near the 3′ end. Primer sequences used were as follows: IVS17-1677C > A FL-primer: 5′-TTTTTGGGCGGTAAAT ACACGTCTCTCGAG-3′; IVS17-1677C > A FS-primer: 5′-CCGCGGTAAATACACGTCTCTCGAT-3′; and IVS17-1677C > A reverse-primer: 5′-GTTTCC GTCAGAAC GCTGCACTA-3′.

This primer set allowed distinct discrimination of alleles. For the assay, a genomic DNA sample (10ng) was amplified with 250nM of each primer (two polymorphic forward, and a reverse) in a 10-μl reaction mixture containing 10mM dNTPs, 10mM Tris-HCl, 1.5mM $MgCl_2$, 50mM KCl, 1U Taq DNA polymerase, and 0.5mM fluorescence-labeled dCTP (ROX-dCTP; Perkin-Elmer, Norwalk, CT, USA). The Sd-PCR reaction was carried out in a thermal cycler (Gene-amp system 9600; Perkin-Elmer) with initial denaturalization at 94°C for 4min, followed by 5 cycles of stringent amplification (94°C for 20s, 64°C for 20s, 72°C for 20s) and then 25 cycles at 94°C for 20s, 62°C for 20s, 72°C for 20s), terminating with a 2-min extension at 72°C. Allele discrimination was carried out by electrophoresis and laser scanning of the DNA fragments on an ABI Prism 377 DNA system, using GeneScan Analysis Software ver2.1 (Applied Biosystems, Foster City, CA, USA). To confirm the accuracy of the Sd-PCR method, direct resequencing was carried out using the ABI Prism BigDye Terminator system (Applied Biosystems).

Statistical analysis

Comparisons of Z scores and biochemical markers between the group of individuals possessing one or two chromosomes of the minor A-allele and the group with only the major C-allele encoded at that locus were subjected to analysis. Coefficients of skewness and kurtosis were calculated to test deviation from a normal distribution. Because the clinical and biochemical traits in each genotypic group were normally distributed, we applied Student's *t*-test, using StatView-J4.5 software (SAS Institute, Cary, NC, USA). A P value of less than 0.05 was considered statistically significant.

Results

Association of LRP5 *gene polymorphism in intron 17 with BMD*

We analyzed the genotypes for the *LRP5* IVS17-1677C > A polymorphism (rs3781586 in the National Center for Biotechnology Information [NCBI] dbSNP data-

Table 1. Comparison of background and biochemical data between subjects bearing at least one A allele (AA + CA) and subjects with no A allele (CC) at IVS17-1677 (intron 17)

Items	Genotype (mean ± SD)		*P* value
	CC	CA + AA	
No. of subjects	166	142	
Age (years)	65.1 ± 9.6	65.4 ± 9.9	NS
Height (kg)	151.0 ± 6.2	150.3 ± 6.4	NS
Body weight (kg)	50.7 ± 8.4	50.3 ± 8.1	NS
Lumbar spine BMD (g/cm²)	0.92 ± 0.20	0.87 ± 0.19	0.025
Lumbar spine BMD (Z score)	−0.02 ± 1.42	−0.42 ± 1.43	0.013
Total body BMD (g/cm²)	1.00 ± 0.11	0.96 ± 0.12	0.015
Total body BMD (Z score)	0.50 ± 1.03	0.08 ± 1.09	0.0022
Ca (mg/dl)	9.2 ± 0.43	9.2 ± 0.45	NS
P (mg/dl)	3.4 ± 0.46	3.4 ± 0.48	NS
ALP (IU/l)	183.7 ± 62.6	195.4 ± 71.0	NS
I-OC (ng/ml)	7.6 ± 4.2	8.3 ± 3.7	NS
PD (pmol/μmol of Cr)	36.1 ± 24.7	34.8 ± 12.0	NS
DPD (pmol/μmol of Cr)	7.6 ± 5.2	7.4 ± 2.4	NS
Intact PTH (pg/ml)	35.1 ± 16.4	35.8 ± 16.6	NS
Calcitonin (pg/ml)	22.8 ± 11.1	23.4 ± 11.7	NS
1,25 $(OH)_2D_3$ (pg/ml)	37.5 ± 12.6	34.3 ± 10.4	NS
TC (mg/dl)	198.7 ± 37.5	195.7 ± 39.2	NS
TG (mg/dl)	141.5 ± 81.4	136.8 ± 71.4	NS
Percent fat	32.1 ± 7.9	31.6 ± 7.4	NS
BMI	22.2 ± 3.2	22.2 ± 2.9	NS

Statistical analysis was performed according to the method described in the text
BMD, bone mineral density; Ca, calcium; P, phosphate; ALP, alkaline phosphatase; I-OC, intact-osteocalcin; PD, pyridinoline; DPD, deoxypyridinoline; PTH, parathyroid hormone; TC, total cholesterol; TG, triglyceride; BMI, body mass index; NS, not significant

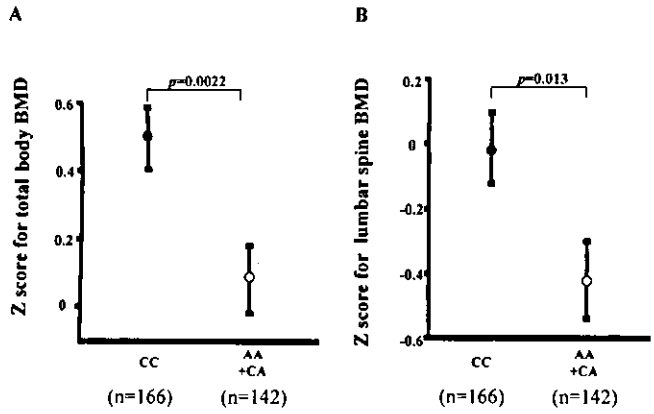

Fig. 1. Z Score values for total body and lumbar bone mineral density (*BMD*) in the groups with each genotype of the *LRP5* gene in intron 17 (IVS17-1677C > A). **A** Z Score values for total body BMD are shown as the *solid circle* for genotype CC at IVS17-1677 and as the *open circle* for genotype AA + CA at IVS17-1677. Values are expressed as means ± SE. Numbers of subjects are shown *in parentheses*. **B** Z Score values for lumbar spine BMD are shown in the same manner as in **A**

base) in 308 subjects, using Sd-PCR methods [25]. Among the 308 postmenopausal volunteers, 24 were AA homozygotes, 118 were CA heterozygotes, and 166 were CC homozygotes. Allelic frequencies were 0.731 for the C allele and 0.269 for the A allele in this population.

We compared Z scores for BMD of total body and lumbar spine between subjects bearing at least one chromosome with the A allele (genotype AA + CA; $n = 142$) and subjects with no A allele (CC; $n = 166$). The former subjects had significantly lower Z scores for total body BMD (0.08 ± 1.09 versus 0.50 ± 1.03; $P = 0.0022$, Fig. 1A) and lumbar BMD (−0.42 ± 1.43 versus −0.02 ± 1.42; $P = 0.013$; Fig. 1B). As shown in Table 1, the background data were not significantly different between these groups.

Discussion

We investigated the influence of a genetic variation of the *LRP5* gene on bone mineral properties. The allelic frequencies of an SNP in intron 17 (0.731 for IVS17-1677C and 0.269 for IVS17-1677A) in Japanese postmenopausal women were in Hardy-Weinberg equilibrium. The allelic frequencies of this SNP in the general Japanese population were reported in the JSNP database (IMS-JST137897). The database reported that the allelic frequencies were 0.726 for IVS17-1677C and 0.274 for IVS17-1677A, indicating that the allelic frequencies in the present study were in line with the JSNP database.

Recently, patients with homozygous *LRP5* gene disruption were reported [20]. There are many types of mutations affecting bone mass accrual during growth, causing the autosomal recessive disorder osteoporosis-pseudoglioma syndrome. Regarding the effect on the bone, these patients showed a marked decrease in their BMD. In addition, Kato et al. [21] created and characterized *LRP5* gene knockout mice. Interestingly, *LRP5* gene knockout mice showed lower bone mass density than wild-type mice because of decreasing osteoblast proliferation. In their report, Kato et al. [21] observed the presence of LRP5 protein in osteoblasts lining the endosteal and trabecular bone surfaces, but not in osteoclasts, by immunohistochemistry in wild-type mice. Recently, a gain-of-function mutation (G171V) in the *LRP5* gene was described in two kindreds with an enhanced bone density [22,23]. In vitro studies showed that the normal inhibition of Wnt signaling by another protein, Dickkopf-1 (Dkk1), was defective in the presence of this mutation, resulting in increased signaling due to unopposed Wnt activity. Thus, LRP5 may be one of the cellular mediators involved in bone formation, by regulating the proliferation and differentiation of osteoblasts.

In the present study, significant correlation was observed between BMD and a polymorphism in intron 17 (IVS17-1677C > A). To our knowledge, this is the first report that a common SNP in the *LRP5* gene affected BMD. However, it is still unclear how BMD is affected by this intronic polymorphism of the *LRP5* gene. For explaining this, three hypotheses could be proposed. (i) This intronic polymorphism may be linked with exon mutations and may contribute to changing LRP5 protein function. (ii) This polymorphism may be linked with mutations of regulatory elements and may affect the levels of expression through transcriptional regulation. (iii) The polymorphism in the *LRP5* gene may be linked with mutation of another unidentified gene adjacent to the *LRP5* gene which causes low BMD directly or indirectly.

In conclusion, our finding suggests that the *LRP5* gene may be a candidate for the genetic determinants of BMD in postmenopausal women. Examining *LRP5* gene variation will, it is hoped, enable us to understand one of the mechanisms of involutional osteoporosis. Wnt and LRP5 signaling have been implicated in other diseases, including cholesterol and glucose metabolism-related diseases [26]. The variant presented here may be involved in the risk of such diseases, as well as osteoporosis.

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Total Hip Arthroplasty with Bulk Femoral Head Autograft for Acetabular Reconstruction in DDH

Surgical Technique

BY SENEKI KOBAYASHI, MD, PHD, NAOTO SAITO, MD, PHD, MASASHI NAWATA, MD, HIROSHI HORIUCHI, MD, RICHARD IORIO, MD, AND KUNIO TAKAOKA, MD, PHD

Investigation performed at the Department of Orthopaedic Surgery, Shinshu University School of Medicine, Matsumoto, Japan, and the Department of Orthopaedic Surgery, Lahey Clinic, Burlington, Massachusetts

The original scientific article in which the surgical technique was presented was published in JBJS Vol. 85-A, pp. 615-621, April 2003

INTRODUCTION

The long-term results of total hip arthroplasty performed with cement and use of a bulk autograft for acetabular reconstruction in patients with developmental dysplasia of the hip have varied considerably. The reported series and literature reviews have indicated that total hip arthroplasties performed with such augmentation can provide excellent long-term results in patients forty-eight years of age and older when coverage of the socket by the graft does not exceed 50%. When it is not possible to achieve >50% coverage of the socket by the ilium at the level of the true acetabulum, more proximal placement of the socket is recommended to obtain adequate coverage. Here we describe the technical details of the avoidance of excessive (≥50%) graft coverage of the socket by additional proximomedial reaming, which is a compromise between the low anatomical placement of the socket with a bulk autograft[1] and the high-hip-center technique without restoration of bone stock[2].

SURGICAL TECHNIQUE

Preoperative radiographic planning with use of transparent socket templates is first performed to evaluate the position of the socket and its coverage by autograft (Fig. 1). When coverage of the most proximal point (apex) of the socket by the ilium cannot be achieved at the low anatomical level, a more proximal placement of the socket is considered to ensure that the apex is covered.

The original Charnley technique, including a lateral approach with a trochanteric osteotomy[3], is employed (Fig. 2). In the series that was the subject of our original report, the original Charnley prosthesis

ABSTRACT

BACKGROUND:
The long-term results of total hip arthroplasty performed with cement and use of a bulk autograft for acetabular reconstruction in patients with developmental dysplasia of the hip have varied considerably. We evaluated the results of total hip arthroplasties performed with acetabular bulk autograft to identify the factors that influence the results of this procedure.

METHODS:
Acetabular roof defects secondary to developmental dysplasia of the hip were reconstructed with a bulk femoral head autograft at the time of total hip arthroplasties performed with use of the Charnley technique and prosthesis. Thirty-seven hips in thirty patients (mean age at the time of the operation, fifty-seven years) were followed for ten to twenty-six years (mean, nineteen

continued

ABSTRACT | continued

years). The Crowe classification of hip subluxation or dislocation was Group II for sixteen hips, Group III for seventeen, and Group IV for four.

RESULTS:
Coverage of the socket by the graft ranged from 5% to 49% (mean, 33%). Twenty-nine sockets were located within the true acetabulum, and eight were placed more proximally. At the time of the latest follow-up, all of the patients had an excellent clinical result, all of the grafts had united, and no hip had radiographic evidence of failure of the fixation.

CONCLUSIONS:
We found that total hip arthroplasty performed with cement and use of a bulk autograft to reconstruct an acetabulum with severe bone deficiency secondary to developmental dysplasia of the hip can provide long-term success in patients forty-eight years of age and older when coverage of the socket by the graft does not exceed 50%. When it is not possible to achieve >50% coverage of the socket by the ilium at the level of the true acetabulum, more proximal placement of the socket to obtain adequate coverage is recommended.

(Charles F. Thackray, Leeds, United Kingdom) was fixed with cement in each patient. An effort should be made to place the socket at the level of the true acetabulum. After reaming of the true acetabulum with the smallest reamer in the transverse direction down to the floor of the acetabular fossa and then maximizing the acetabulum within the limitation of its anteroposterior width with progressively larger reamers, a socket size-gauge is used to determine the coverage of the socket by iliac bone. If ≥5 mm of the superior portion of the socket cannot be contained by bone, the decision to use a graft is made, according to the recommendation of Charnley and Feagin[1].

However, when the assessment with the socket size-gauge indicates that the most proximal point (apex) of the socket cannot be covered by the ilium, proximomedial reaming is performed to obtain such coverage (Fig. 2, *C* and *D*). This additional reaming is accomplished by shifting the direction of a hemispherical reamer proximally, from medial (transverse) to proximomedial, until the most proximal point of the socket size-gauge is covered by the ilium. The radiographs, operative photographs, and their schematic representations in Figures 1 and 2 demonstrate how this additional proximomedial reaming allows coverage of the apex of the socket by the ilium. The defective part of the acetabulum (usually the superolateral aspect of the true acetab-

CRITICAL CONCEPTS

INDICATIONS:
During the index period, the decision to use a bulk femoral head autograft was made when ≥5 mm of the superior portion of the socket could not be contained by bone, according to the recommendation of Charnley and Feagin[1]. On discharge radiographs, all of the sockets in the study group were seen to be contained by a composite of iliac bone and autografted femoral head bone. After the index period, we expanded the indications for this procedure. Now, when both complete containment of the socket by bone and a horizontal cement-bone interface at the level of the acetabular roof cannot be obtained after reaming, we use a bulk autograft to obtain these goals. Complete osseous containment of the cemented socket has been shown to be important for durability[6]. The advent of a socket with a flange for high-pressure cement injection in 1979 allowed filling of bone deficiencies of the acetabular roof with cement as shown in the right hip in Figure 3. However, the long-term results revealed that this was a misusage of the flanged socket. Figure 3, *B*, shows the obliquity of the cement-bone interface in the roof part of the right acetabulum compared with the horizontal interface in the left acetabulum, which was reconstructed with a bulk autograft. When complete containment of the socket by bone and a horizontal area in the roof are not obtained after reaming, we recommend bone-grafting to obtain these goals.

CONTRAINDICATIONS:
When a bone defect is not localized superolaterally and diffuse, extensive bone loss is encountered in the acetabulum (as in revision cases), this procedure may not be sufficient to reconstruct the acetabulum. In that situation, larger, more structural grafts may be necessary to restore column integrity or acetabular reconstruction cages may be considered.

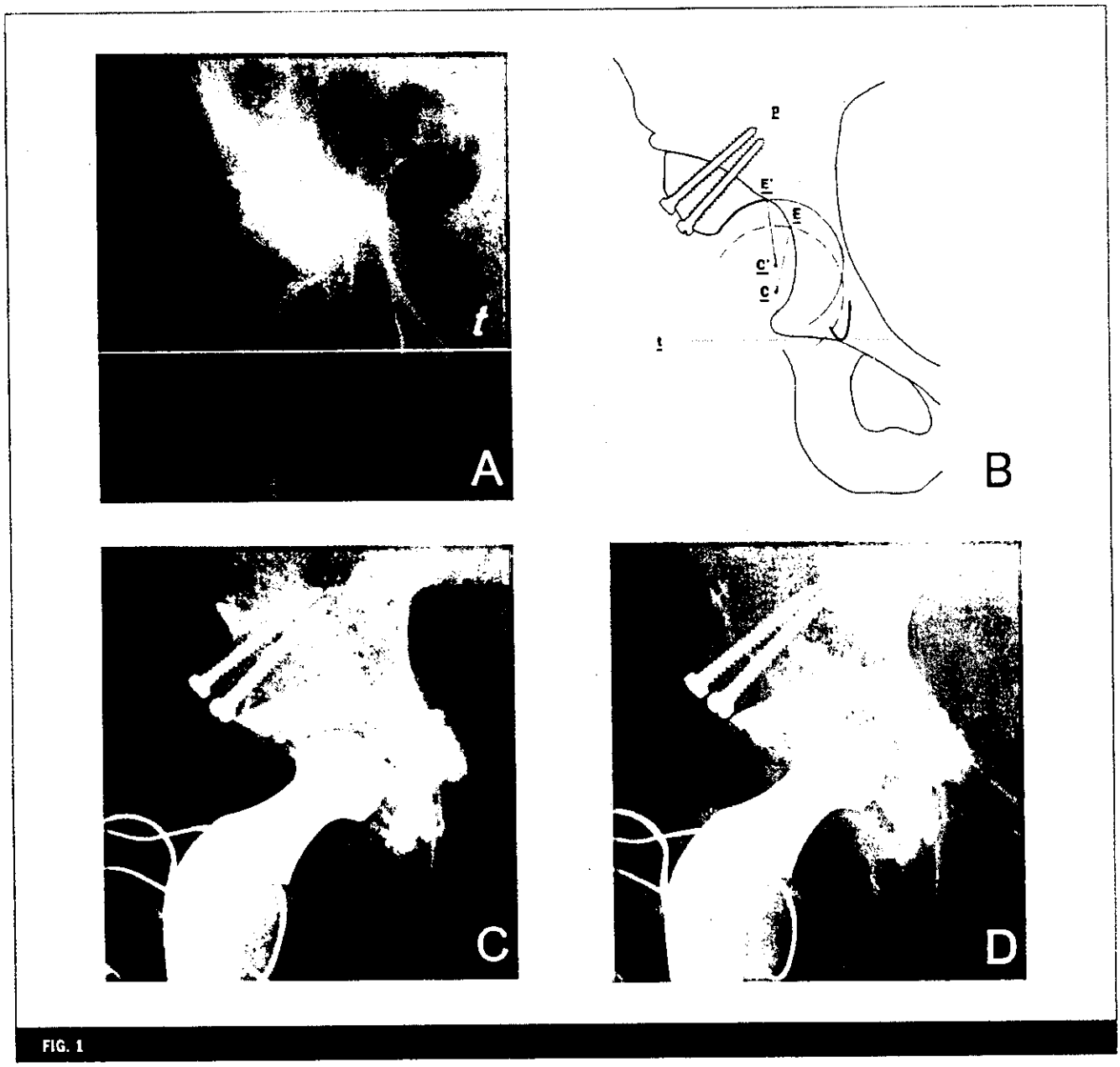

FIG. 1

A fifty-seven-year-old woman underwent a right total hip arthroplasty with acetabular bone grafting. *A:* Preoperative radiograph showing Crowe Type-II subluxation and normotrophic osteoarthrosis of the right hip (*t* = teardrop line [a line drawn through the distal ends of both teardrops]). *B:* Schematic representation of radiographs showing the expected socket position with acetabular reaming at the low anatomical level (dashed semicircle; C = hip center and E = proximal edge of the reamed acetabulum) and that with additional proximal reaming (solid semicircle; C' = hip center and E' = proximal edge of the reamed acetabulum). Line p (drawn perpendicularly to t and through the hip center) indicates that the most proximal point (apex) of the socket cannot be covered by the ilium with the low anatomical reaming and the socket center-edge angle becomes minus. It also indicates that additional proximal reaming allows coverage of the apex of the socket by the ilium with a plus socket center-edge angle. *C:* Discharge radiograph showing the socket fixed with a bulk autograft that covers 41% of it. Although the socket center-edge angle is 1°, the most proximal point of the socket is contained by the iliac bone via bone cement and is not supported by graft. The height of the hip center is 14 mm, and the socket is in the true acetabulum. *D:* Radiograph made twenty-three years after the index procedure, showing no demarcation around the socket (Hodgkinson Type 0). Polyethylene wear was measured to be 2.0 mm (wear rate, 0.087 mm/yr).

FIG. 2

Photographs of the right acetabulum during the procedure. With the patient in the supine position, the upper and right margins of each photograph are anterior and proximal to the acetabulum, respectively. *A:* Drawing of the lateral side of the pelvis, indicating the visual field of Figs. *B* through *G*. *B:* The exposed false acetabulum, which is flat and shallow. *C:* After reaming of the acetabulum and preparation of the acetabular roof for bone-grafting. *D:* Schematic representation of Fig. *C*. The dashed circle indicates reaming at the low anatomical level with its center at point C. The solid circle represents additional reaming with its center (C') shifted proximally. The lightly shaded area is the defective roof part of the false acetabulum, which has been prepared with surface reaming and drilling of multiple holes (2.8 or 3.2 mm in diameter). *E:* After fixation of a bulk autograft to the bone bed and drilling of multiple anchor holes. F: Schematic representation of Fig. *E*. The darkly shaded area is the autograft fixed with two screws. M = multiple anchor holes (6.0 mm in diameter). P = pubic anchor hole, and I = ischial anchor hole. *G:* After fixation of the socket with cement.