266 women) with all of the required data, including examinations and completed questionnaires at both the time of enrollment and at 6-month follow-up, were included in the present study. Among the included cases, history of steroid use was confirmed in 36 patients (11.6%). Forty-four patients (14.2%) developed additional fractures during follow-up. Five patients underwent surgical treatment (4 vertebroplasty and 1 posterior decompression). At the time of enrollment, patients were examined using plain radiography and MRI of the spine. Calcaneal bone quality was evaluated in quantitative ultrasound measurements using a speed of sound (SOS) parameter. Severity of pain was assessed subjectively by patients using a visual analog scale (VAS). The Short Form-36 (SF-36) questionnaire was applied to assess QOL. To evaluate ADL, we used criteria for evaluation of the degree of independence (severity of bedridden state) during daily living for disabled elderly individuals as proposed by the long-term care insurance system of the Japanese Health and Welfare Ministry (Fig. 1). At the final visit after the 6-month follow-up, all patients were re-examined using plain radiography and MRI. The SF-36 was also readministered to assess patient QOL.

Overall, 208 patients were hospitalized for several days during the acute phase and 102 were treated on an outpatient basis. In addition, 280 patients were treated with some kind of corset (tailor-mode hard corset, n=61; tailor-mode elastic corset, n=158; ready-made elastic corset, n=61) and 30 did not wear any corset. These treatment options were decided by the individual doctors in each hospital based on their experience. All doctors were specialist orthopedic surgeons. We therefore considered these treatment options as standard conservative treatment for OVF at the time of enrollment in Japan.

ADL assessment

The criteria of the Japanese long-term care insurance system use four different ranks, each containing two different categories (Fig. 1). We classified patients into these four ranks: independent life; requires assistance to leave home; nearly bedridden; and completely bedridden. We defined reduced ADL as a reduction of □1 single grade by the 6-month follow-up after fracture.

Radiological assessment

For vertebral collapse of the fractured vertebra, we calculated the collapsing ratio of vertebral body at the time of enrollment as well as at the 6-month follow-up. (Fig. 2A). Middle column injury of the fractured vertebral body was judged by protrusion of the posterior wall of the vertebral body into the spinal canal on mid-sagittal MRI at the time of enrollment(Fig. 2B). Non-union was defined as the presence of an intravertebral cleft on plain radiography, which was performed with the patient in a supine position, at the 6-month follow-up. (Fig. 2C).

Statistical analysis

Reduced ADL was defined as an outcome measure. Explanatory variables included age, sex, body mass index (BMI), bone mineral density (BMD), pain VAS, level of fracture, collapsing ratio, middle column injury, previous spine fractures, regular exercise before fracture and use of a corset. We defined regular exercise as daily or regular activity (more than several times a month) such as walking, jogging or participating in various sports for the past year. Continuous variables (age, VAS, collapsing ratio) were categorized by approximate tertile, except for BMI and BMD. BMI was divided into three categories: thin, BMI <18.5; normal, BMI □18.5 but <25; and obese, BMI ≥25. BMD was divided into two categories as follows: low, defined as SOS <1482 m/s (T-score=-1.63) for men and <1479 m/s (T-score=-1.79) for women (representing a BMD<70% of young adult mean); and normal, defined as SOS ≥1482 m/s for men and ≥1479 m/s for women. Levels of fracture were divided into two categories: thoracolumbar junction level, T11-L2; and other spinal level. Previous spine fractures were divided into three categories: absence of previous vertebral fracture; 1 previous vertebral fracture; and □2 previous vertebral fractures. Other characteristics were examined as dichotomous variables (sex, male/female; middle column injury, present/absent; regular exercise before fracture, present/absent; and use of a corset, present/absent).

To elucidate factors predicting reduced ADL, uni- and multivariate statistical analyses was performed. Odds ratios (ORs) and 95% confidence intervals (CIs) for the occurrence of reduced ADL were calculated as approximations of the relative risk estimates. Factors included in the multivariate model were age, sex, BMI, BMD, pain VAS, level of fracture, collapsing ratio, middle column injury, previous spine fractures, regular exercise before fracture and use of a corset. Also, to clarify the effects of prognostic factors on reduced ADL, we analyzed relationships between significant prognostic factors for reduced ADL and factors (pain VAS, SF-36 score and radiological factors) at the 6-month follow-up. Differences between groups were assessed using *t*-tests. All analyses were performed using Statistical Analysis System version 9.1 software (SAS Institute, Cary, NC, USA). Findings of $P<0.05$ were considered significant.

RESULTS

Table 1 shows demographic data for patients at the time of enrollment. Mean age at the time of enrollment was 75.8 years (range, 65-93 years). Mean BMI was 22.1 kg/m^2. Mean SOS values on quantitative ultrasonography were 1484.1 m/s (T-score=-1.54) for men (range, 1397 (T-score=-4.03)-1558 (T-score=0.57) m/s) and 1472.2 m/s (T-score=-1.99) for women (range, 1428 (T-score=-3.33)-1543 (T-score=0.15) m/s). Mean VAS score for back pain was 8.3. Fracture in the thoracolumbar spine was seen in 242 of 310 patients (78.1%), while 121 of 310 patients (39.0%) had previous spine fractures. Forty-seven of the 121 patients (38.8%) had previous fractures adjacent to the fresh fracture. Middle column injury of the vertebral body was observed in 96 of 310 patients (31.0%). Mean anterior vertebral column collapsing ratio of the fractured vertebra, as calculated in Figure 2, at the time of entry ranged from 25 to 100%, with an average of 82.6%.

Kyphotic angle of the fractured vertebra (Fig. 2A) at the time of entry ranged from -6 to 33 degrees, with an average of 9.3 degrees. Eighty-eight of 310 patients (28.4%) performed regular exercise before fracture. Use of a corset had been prescribed for 280 of 310 patients (90.3%).

In terms of ADL before fracture, 291 patients showed independent living, 18 patients required assistance leaving home (5.8%) and 1 patient was nearly bedridden (0.3%). For ADL at the 6-month follow-up, 232 patients showed independent living (74.8%), 58 patients required assistance leaving home (18.7%), 16 patients were nearly bedridden (5.2%), and 4 patients were completely bedridden (1.3%) (Table 2). The frequency of reduced ADL at the time of the 6-month follow-up was 21.3% (66 of 310).

The results of uni- and multivariate analysis to identify prognostic factors for reduced ADL are shown in Table 3. In univariate analysis, age >75 years (OR, 1.04; 95%CI, 1.001-1.08; P=0.044), female sex (OR, 3.03; 95%CI, 1.04-8.82; P=0.041), □2 previous spine fractures (OR, 2.42; 95%CI, 1.24-4.73; P=0.009), presence of a middle column injury (OR, 1.90; 95%CI, 1.08-3.34; P=0.021), and a lack of regular exercise before fracture (OR, 3.59; 95%CI, 1.64-7.87; P=0.001) were significantly associated with reduced ADL. In multivariate analysis, presence of middle column injury (OR, 2.26; 95%CI, 1.12-4.56; P=0.022) and lack of regular exercise before fracture (OR, 2.49; 95%CI, 1.08-5.71; P=0.030) were significantly associated with reduced ADL.

To examine the effects of prognostic factors on reduced ADL, we compared the presence of middle column injury group with the absence of middle column injury group in terms of pain VAS, SF-36 score, collapsing ratio and frequency of non-union at 6 months. Collapse of the vertebral body was significantly more prominent in the presence of middle column injury group than in the absence of middle column injury group. Frequency of non-union and pain VAS scores were significantly higher in the presence of middle column injury group than in the absence of middle column injury group. However, with the SF-36, physical component score (PCS) and mental component score (MCS) showed no significant differences between groups. Similarly, we compared the presence of regular exercise group with the absence of regular exercise group. PCS from the SF-36 was significantly lower in the lack of regular exercise group than in the presence of regular exercise group. However, VAS score, collapsing ratio and frequency of non-union showed no significant differences (Table 4).

DISCUSSION

OVF has severe effects on ADL and QOL in elderly patients and can be the beginning of a long-lasting deterioration in health[4]. This prospective clinical study was designed to identify factors predicting reduced ADL following OVF, with the aim of preventing impaired ADL after OVF. The percentage of patients with reduced ADL following OVF by 6 months was 21.3% in the present study. Prognostic factors inducing impairment of ADL following osteoporotic vertebral fractures were the presence of middle column injury of the fractured vertebral body and a lack of regular exercise before fracture.

Progression of vertebral body collapse is reportedly caused by middle column injury of the vertebral body[18]. We have reported in another study that non-union following OVF occurred more frequently in cases with involvement of the vertebral posterior wall[19]. In the present study, collapse of the vertebral body was significantly more prominent in cases with middle column injury than in cases without middle column injury. The frequency of non-union and pain VAS scores were also significantly higher in cases with middle column injury than in cases without middle column injury. This indicates that middle column injury of the vertebral body in cases of OVF represents a prognostic factor for continued progression of vertebral body collapse and non-union. Middle column injury also caused prolonged back pain and impairment of ADL.

Increasing evidence suggests that exercise is an effective strategy for the treatment of osteoporosis[20]. A randomized controlled trial of women with vertebral fractures found that exercise was associated with reduced pain and improvements in back muscle strength and quality of life[21]. Several studies have reported spinal back extensor strength and lumbar spinal mobility as the most important factors for QOL in osteoporotic patients, so exercise strengthening back extensors may effectively prevent deterioration of QOL[22,23]. Papaioannou et al. reported that home-based exercises (i.e., walking) improved QOL in elderly women with osteoporosis-related vertebral fractures[24]. However, few previous studies have examined whether regular exercise before fracture prevents reductions of ADL following OVF. In the present study, patients with lack of regular exercise before fracture showed significantly higher risk of reduced ADL following OVF. At the 6-month follow-up, PCS of the SF-36 was lower in patients without regular exercise than in those participating in regular exercise. Regular strength training seems to prevent loss of muscle function[25]. We speculate that patients with regular exercise are less affected by disuse atrophy of the muscles during the initial phase following fracture. Based on these findings, regular exercise should be encouraged to prevent reduced ADL following OVF, particularly for elderly individuals.

In this study, prognostic factors inducing reduced ADL were the presence of middle column injury of the vertebral body at the time of injury and lack of regular exercise before fracture. These findings are helpful in determining treatment options for patients with osteoporotic vertebral fractures. Other treatment options such as vertebroplasty in addition to conventional conservative treatment might thus be necessary in the early stage after fracture for patients showing these prognostic factors.

A key limitation in this study was the short follow-up of 6 months. In a report that analyzed the status of 1,010 women at 6 years after vertebral fracture, those with a previous fracture showed up to seven times greater likelihood of reporting difficulties with a variety of activities compared to those without such a history[26]. Nevitt et al. reported that the relative risk of back pain and limitation of activity increased with the number of vertebral fractures[5]. However, in our study, history of previous fracture did not represent a significant predictor of reduced ADL. This might be due to the short follow-up in the present study. The presence of multiple vertebral fractures may be associated with effects on ADL at a longer follow-up.

In conclusion, we investigated factors predicting reduced ADL following OVF. Reduced ADL at 6 months after OVF was 21.3% in the present prospective study. Prognostic factors significantly associated with reduced ADL were the presence of middle column injury of the vertebral body at the time of injury and lack of regular exercise before fracture.

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Independent life	Rank J	Although some disability is present, daily life is almost independent and the patient can go out without needing assistance from other individuals. 1. Goes out using means of transportation, etc. 2. Goes out in the vicinity of home.
Requires assistance to leave home	Rank A	Lives independently indoors, but requires assistance to go out. 1. Goes out with assistance, stays out of bed most of the day 2. Seldom goes out, has several rests in bed during the day
Nearly bedridden	Rank B	Requires some assistance living indoors and spends most of the day in bed, but keeps sitting up. 1. Uses a wheelchair to move about, but gets up for meals and to go to the toilet 2. Moves about in a wheelchair with assistance
Completely bedridden	Rank C	Spends all day in bed and requires assistance to urinate/defecate, and with meals and dressing. 1. Can turn over in bed unassisted 2. Cannot turn over in bed unassisted

Figure 1. Criteria for evaluating the degree of independence (severity of bedridden state) during daily living for disabled elderly individuals

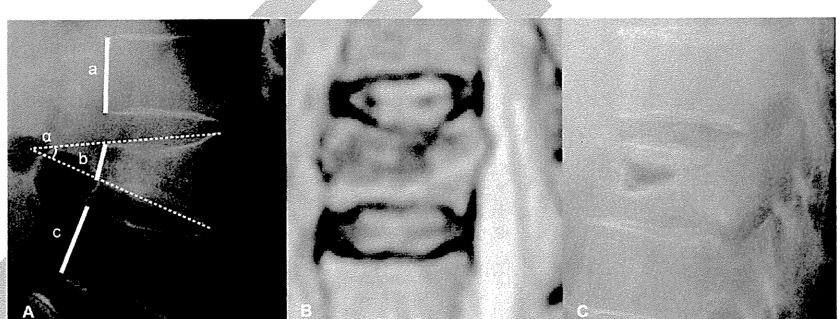

Figure 2. Radiological assessment. **A)** Anterior vertebral collapsing ratio = 2b/(a+c) 100%. Kyphotic angle = α degrees **B)** Middle column injury of the fractured vertebral body was judged by protrusion of the posterior wall of the vertebral body into the spinal canal on mid-sagittal MRI. **C)** Non-union was defined as the presence of an intravertebral cleft on plain radiography.

Table 1: Demographic date at the time of enrolment (n=310)

Variable		Mean (SD), Range or Number (%)
Age (years)		75.8 (6.4), 64-93
Sex(male/female)		44/266
BMI (kg/m^2)		22.1 (3.5), 14.2-34.2
BMD (m/s)	Male	1484.1 (23.8) (T-score=-1.54), 1397-1558
	Female	1472.2 (22.3) (T-score=-1.99), 1428-1543
VAS score		8.3 (2.0), 1.8-10.0
Thoracolumbar junction level		242 (78.1)
Previous spine fracture		121 (39.0)
Middle column injury		96 (31.0)
Collapsing ratio (%)		82.6 (14.3), 25-100
Regular exercise before fracture		88 (28.4)
Use of corset		280 (90.3)

Table 2: Rank of ADL (n=310)

	Rank J	Rank A	Rank B	Rank C
pre-fracture	291	18	1	0
at 6 months	232	58	16	4
Rank J: Independent life Rank A: Requires assistance to leave home Rank B: Nearly bedridden Rank C: Completely bedridden				

Table 3: Uni- and multivariate ORs for reduction of ADL

	Reduction of ADL		Univariate		Multivariate	
Variables	(+) n=66	(-) n=244	OR (95%CI)	P	OR (95%CI)	P
Age (years)						
≤75	27	130	1		1	
>75	39	144	1.04 (1.001-1.08)	0.044	1.02 (0.97-1.07)	0.343
Sex						
Male	4	40	1		1	
Female	62	204	3.03 (1.04-8.82)	0.041	2.45 (0.78-7.64)	0.120
BMI (kg/ m^2)						
Normal	37	173	1			

Thin (BMI <18.5)	14	34	1.92 (0.94-3.94)	0.073	1.50 (0.67-3.35)	0.318
Obese (BMI ≥25)	13	36	1.68 (0.81-3.49)	0.157	1.52 (0.66-3.49)	0.316
BMD						
Normal	17	98	1		1	
Low	45	144	1.80 (0.97-3.33)	0.06	1.56 (0.76-3.20)	0.216
VAS score						
≤9.0	33	129	1		1	
>9.0	33	115	1.004 (0.87-1.15)	0.955	0.95 (0.82-1.11)	0.570
Level of injury						
Other level	18	244	1		1	
Thoracolumbar level	48	194	0.68 (0.36-1.28)	0.239	0.68 (0.33-1.42)	0.311
Previous spine fracture						
Absent	33	156	1		1	
One fracture	14	51	1.29 (0.64-2.61)	0.466	0.97 (0.44-2.12)	0.948
Two or more fractures	19	37	2.42 (1.24-4.73)	0.009	1.83 (0.84-4.10)	0.137
Middle column injury						

Absent	38	176	1		1	
Present	28/	68	1.90 (1.08-3.34)	0.024	2.26 (1.12-4.56)	0.022
Collapsing ratio (%)						
≥84	30	128	1		1	
<84	36	116	0.99 (0.97-1.009)	0.292	0.98 (0.96-1.01)	0.235
Regular exercise before fracture						
Present	8	80	1			1
Absent	58	164	3.59 (1.64-7.87)	0.001	2.49 (1.08-5.71)	0.030
Use of corset						
Present	57	223	1			1
Absent	9	21	1.67 (0.72-3.86)	0.224	2.08 (0.77-5.58)	0.144
OR, odds ratio; CI, confidence interval.						

Table 4: Comparison of VAS, SF-36 score, collapsing ratio of vertebral body and non-union rate at 6 months in each group (presence/absence of middle column injury and regular exercise before fracture)

		Middle column injury			Regular exercise		
		(+) (n=96)	(-) (n=214)		(+) (n=88)	(-) (n=222)	
VAS score		3.7	2.7	P=0.002	3.0	3.0	NS
SF-36 score	PCS	23.8	28.3	NS	33.5	24.2	P<0.001
	MCS	49.0	50.3	NS	51.3	49.4	NS
Collapsing ratio		51.5%	67.9%	P<0.001	64.0%	62.3%	NS
Non-union rate		25.0%	8.4%	P<0.001	11.4%	14.0%	NS
NS, not significant; PCS, physical component score; MCS, mental component score.							

Cellularity and Cartilage Matrix Increased in Hypertrophied Ligamentum Flavum

Histopathological Analysis Focusing on the Mechanical Stress and Bone Morphogenetic Protein Signaling

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Study Design: Histopathological and immunohistochemical analysis.

Objective: To investigate the histological changes and expression of bone morphogenetic protein (BMP) signaling component in hypertrophied ligamentum flavum (LF), and to clarify the effect of mechanical stress on them.

Summary of Background Data: Hypertrophic changes of the LF are a major factor in degenerative lumbar canal stenosis (DLCS), but their mechanism remains unclear. BMPs are growth factors that regulate many cellular processes including proliferation, differentiation, and extracellular matrix synthesis. However, a few studies have investigated the expressions of BMP signaling in the hypertrophied LF.

Methods: A total of 133 LF specimens from patients with DLCS and 17 control LF specimens from patients with lumbar disc herniation were analyzed histologically using hematoxylin and eosin, elastica van Gieson, and toluidine blue staining. To analyze the influence of mechanical stress, the DLCS specimens were divided into 2 groups: DLCS with and DLCS without hypermobility groups. The LF thickness was measured by magnetic resonance image, and the correlations between the thickness and the histological data were analyzed. Immunohistochemical analyses were carried out to confirm the expressions and localizations of BMP signaling components.

Results: The cell number and cartilage matrix area were significantly increased in the hypertrophied LF, and those changes were more obvious in DLCS with hypermobility than in DLCS without hypermobility. The cellularity and percentage of cartilage matrix area had positive linear correlations with the LF thickness. BMP receptors and BMP ligands were both expressed by many cells of the hypertrophied LF, and some of these cells were positive for Sox9, CD105, and Msx2. The percentage of immunopositive cells for each BMP receptor type was significantly higher in DLCS with hypermobility than in DLCS without hypermobility.

Conclusions: Higher cellularity and increased cartilage matrix area are important changes in LF hypertrophy. These results suggest that BMP signaling and mechanical stress may play a role in the hypertrophied LF.

Key Words: ligamentum flavum, degenerative lumbar canal stenosis, cartilage matrix formation, bone morphogenetic protein, mechanical stress

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Degenerative lumbar canal stenosis (DLCS) is the most common spinal disorder among the elderly population. Hypertrophic changes of the ligamentum flavum (LF) are one of the major factors of canal stenosis in the lumbar spine.[1] Earlier studies have focused on the morphologic and histological changes of the hypertrophied LF, such as loss of elastic fibers, increase in collagenous fibers, calcification, and ossification.[2–5] However, the exact mechanism of LF hypertrophy has not been well elucidated.

Mechanical stress is considered to be one of the important factors for LF hypertrophy. Fukuyama et al[6] reported that an LF with radiological degenerative signs such as spondylolisthesis or vacuum phenomenon exhibits severe hypertrophy, and suggested that mechanical instability may be a possible cause of LF hypertrophy. However, the precise mechanism for the correlation between clinical instability and hypertrophy remains unclear.

Several earlier studies have shown the involvement of transforming growth factor (TGF)-β1 in the process of hypertrophic changes of the LF.[7–9] Park et al[8] reported that the concentration of TGF-β1 is much higher in a hypertrophied LF than in a control LF. Sairyo et al[9]

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