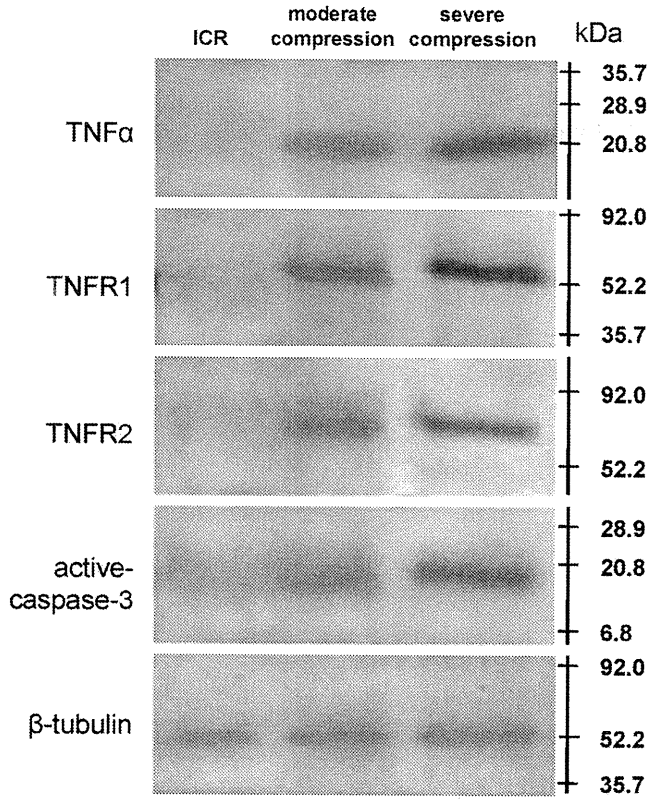

Figure 6. Immunoblot analysis showing overexpression of TNF-α, TNFR1, TNFR2, and active-caspase-3 in the *twy/twy* mouse with moderate and severe spinal cord compression. The major molecular bands detected were 19 kDa in TNF-α, 55 kDa in TNFR1, 81 kDa in TNFR2, and 17 kDa in active-caspase-3. The same blot was stripped and reprobed with β-tubulin antibodies as internal loading control (β-tubulin; 52 kDa). Representative results of 3 experiments with similar results.

sections revealed that most of the identified apoptotic cells in the white matter were oligodendrocytes (population 78 ± 14%) while others included microglia and astroglial cells. Shuman *et al*[33] and Koda *et al*[27] reported similar findings in different trauma models of spinal cord injury. Though insignificant when compared with the acute spinal cord injury, the longitudinally diffuse and extensive pattern of oligodendrocyte apoptosis in *twy/twy* mouse may be similar to the secondary damage process observed after acute trauma, and it was very interesting that increment in the number of apoptotic cells in this mouse model was proportional to the magnitude of chronic external compression.

A variety of signal transduction pathways are involved in the complex process of apoptosis.[12,34] Caspases are a family of cysteine proteases that play important roles in the effector phase of apoptosis and are activated through intrinsic and extrinsic pathways. Previous studies reported that spinal cord injury resulted in the induction of apoptosis mediated by caspase-3[35] and increased expression of the death receptors, especially Fas and p75 receptors.[36] The p75 neurotrophin receptors play a role in not only the promotion of neuronal cell death[37] but also neuronal survival.[38] On the other hand, the extrinsic pathway is initiated by ligand of cell surface death receptors belonging to the TNF/nerve growth factor receptor superfamily.[39] Recent studies have described overexpression of TNF-α in apoptotic neuronal and glial cells including microglia in spinal cord injury and suggested it was the cytokine that triggers oligodendrocyte apoptosis, though the source of this TNF-α in injured spinal cord was not clear.[19,40] A previous study suggested that activated microglia secrete various cytotoxic factors including TNF-α in response to axonal regeneration and induce apoptosis of oligodendrocytes. It was also reported that the population of apoptotic cells following spinal cord contusion comprised oligodendrocytes and possibly phagocytic microglia or macrophages.[33] Double immunofluorescence staining in this study also indicated the expression of TNF-α in local cells including microglia, while the expression of TNFR1 and TNFR2 was identified in apoptotic oligodendrocytes in the segment with the most severe cord compression in the *twy/twy* mice. The discovery and studies of a "death domain" in the TNFR1 and in other related receptors has revealed information on the signaling pathways leading to the activation of caspase-8 and caspase-3, before apoptosis.[41] It seems reasonable to suggest, therefore, that following a traumatic injury to the spinal cord, accumulation of TNF-α may act to initiate an apoptotic cascade *via* receptor-mediated signaling. Although TNFR1 mediates the majority of the apoptotic effects as well as cell surviving signals while TNFR2 predominantly transmits cell-surviving signals, their locations and roles in TNF-α-induced signaling pathway are still not elucidated and controversial.[42] Holmes *et al*[25] described immunocytochemical localization of these receptors: TNFR1 was located on neuronal cells and afferent fibers within the dorsal root ganglion, but TNFR2 immunoreactivity was absent in these locations. On the other hand, Yan *et al*[26] reported possible roles of expression of TNFR1 and TNFR2 in adult rat spinal cord injury. They reported overexpression of TNFR1 and TNFR2 in the spinal cord and that such expression was located on neurons, astrocytes, and oligodendrocytes after spinal cord injury. In chronic spinal cord compression, we found overexpression of both TNFR1 and TNFR2 primarily in oligodendrocytes and the number of those receptor-positive oligodendrocytes increased proportionately with the increased magnitude of mechanical compression in the *twy/twy* mouse. Although this source was not demonstrated in the present study and mechanisms other than those involving TNF-α and TNFRs (TNFR1 and TNFR2) pathway exist for apoptosis of oligodendrocytes,[33] the above results and those of the present study suggest the involvement of certain mechanisms in upregulation of inflammatory cytokines, including TNF-α, and that mechanical compression-induced expression of TNFR1 and TNFR2 may closely contribute to apoptosis, particularly that of oligodendrocytes in *twy/twy* mouse spinal cord with severe compression, a model that simulates cervical compressive myelopathy.

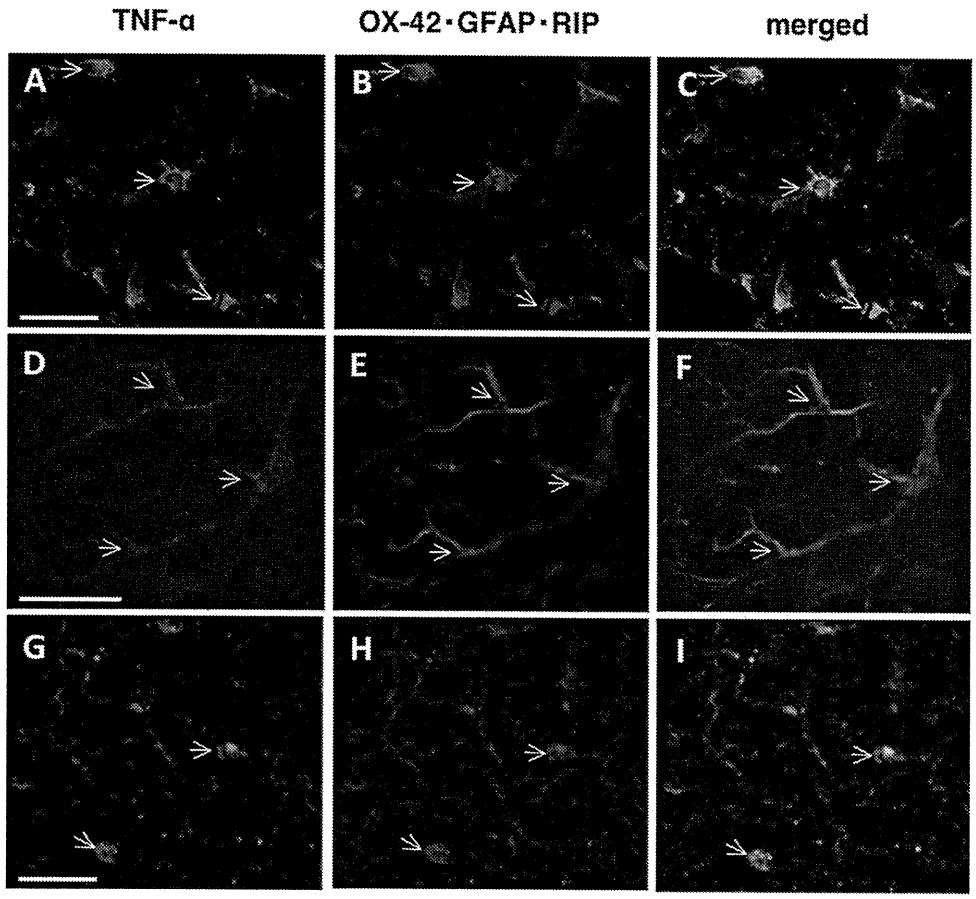

Figure 7. Photomicrographs showing double immunostaining for TNF-α and immunoreactivity for microglia OX-42, astrocyte GFAP and oligodendrocyte RIP in the anterior column at spinal cord level of maximal compression in *twy/twy* mice with severe compression. White arrows in A-I: colocalization of TNF-α, OX-42, GFAP and RIP. Overlap of the markers appears yellow in the third rows. Note the expression of TNF-α in microglia, astrocytes, and oligodendrocytes. Scale bars = 20 μm (**A–F**), 10 μm (**G–I**).

In conclusion, we observed an increased number of TUNEL-positive oligodendrocytes in the white matter of the *twy/twy* mouse spinal cord that was subjected to progressive mechanical compression *vis a tergo* with aging, and the number of these cells increased with the magnitude of compression. Longitudinal topographic mapping of TUNEL-positive cells showed considerable distribution along the spinal cord axis. The results

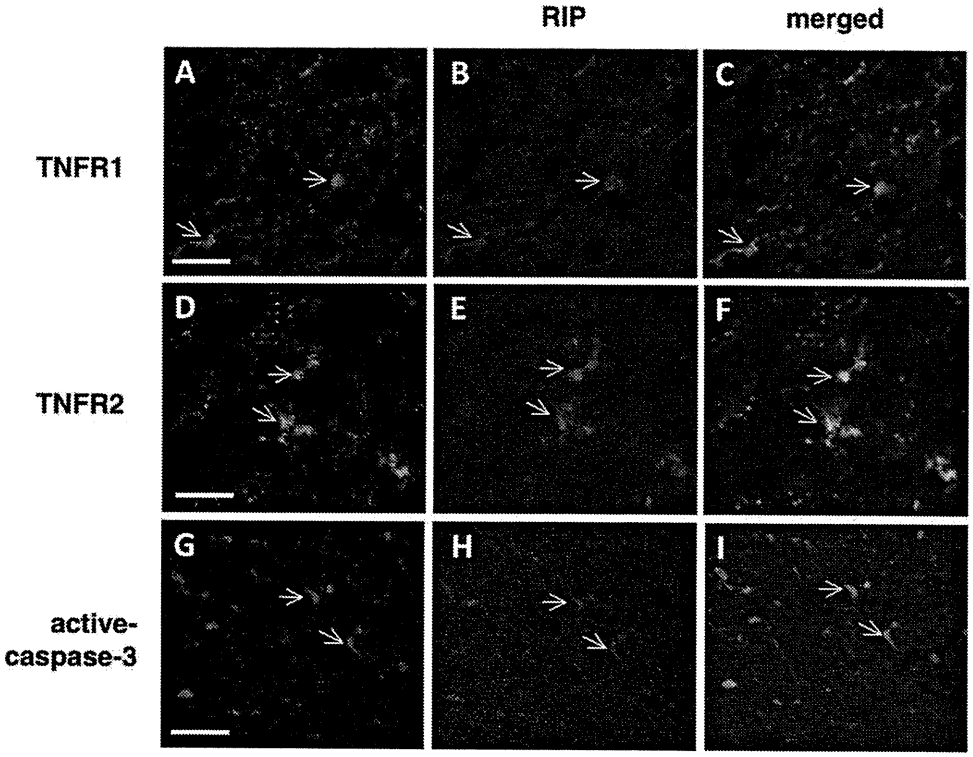

Figure 8. Photomicrographs showing double staining for TNFR1, TNFR2, and active-caspase-3 with immunoreactivity for oligodendrocyte RIP in the anterior funiculus at spinal cord level of maximal compression in *twy/twy* mice with severe compression. White arrows in **A–I**: colocalization of TNFR1, TNFR2, active-caspase-3 and RIP. Overlap of the markers appears yellow in the third rows. Note the expression of TNFR1, TNFR2, and active-caspase-3 in oligodendrocytes. Scale bars = 20 μm.

showed that in the *twy/twy* mouse spinal cord, TUNEL-positive oligodendrocytes were immunoreactive to TNF-α, TNFR1, and TNFR2. These findings suggest that TNF-α, and TNFR1 as well as TNFR2 seem to play at least some roles in the demise of glial cells, which probably contribute to axonal degeneration and demyelination in the *twy/twy* mouse spinal cord with severe compression.

Key Points

- The number of TUNEL-positive cells increased with the magnitude of compression in the *twy/twy* mouse spinal cord with chronic mechanical compression, and the number of TUNEL-RIP double-positive cells in the white matter appeared to increase with severe cord compression.
- TNF-α, TNFR1 TNFR2, and active-caspase-3 were expressed in correlation with the magnitude of compression, while TNF-α was colocalized in OX-42, GFAP and RIP with severe compression.
- TNF-α, and TNFR1 as well as TNFR2 appear to play some roles in the apoptosis of oligodendrocytes, which contribute to axonal degeneration and demyelination in *twy/twy* mice with severe spinal cord compression.

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Effects of Alendronate on Bone Metabolism in Glucocorticoid-Induced Osteoporosis Measured by ^{18}F-Fluoride PET: A Prospective Study

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Osteoporosis represents a significant side effect of glucocorticoid therapy, and alendronate has been reported to prevent this glucocorticoid-induced osteoporosis. Functional imaging with ^{18}F-fluoride PET allows quantitative analysis of bone metabolism in specific skeletal regions. However, only a few studies have quantitatively determined bone turnover and metabolism in glucocorticoid-induced osteoporosis by radiologic imaging techniques including PET. The aim of this study was to examine changes in regional bone remodeling and turnover as measured by ^{18}F-fluoride PET, the relationship between these measured changes and conventional bone metabolism parameters, and the effect of alendronate treatment. **Methods:** The study group consisted of 24 postmenopausal women (mean age, 59.7 y) who had various diseases, excluding rheumatoid arthritis, and had been treated with 10 mg or more of oral glucocorticoids (prednisolone equivalent) per day for more than 6 mo. Treatment with 5 mg of alendronate per day began at the time of study entry and continued for 12 mo. ^{18}F-fluoride PET was performed at baseline, 3 mo, and 12 mo to determine localized bone turnover, and the results were compared with other bone metabolism parameters. **Results:** Lumbar spine standardized uptake values (SUVs) were significantly lower ($P < 0.05$) in the osteoporotic group (T-score ≤ -2.5) than in the group that was healthy or osteopenic (T-score > -2.5). Patients treated with alendronate for 12 mo exhibited significant decreases in serum bone-specific alkaline phosphate ($P < 0.05$), urinary N-telopeptide for type I collagen ($P < 0.01$), lumbar spine SUV ($P < 0.01$), and femoral neck SUV ($P < 0.01$) in association with a gradual increase in bone mineral density (BMD) of the lumbar spine relative to the baseline value ($P < 0.05$). Although there was a significant correlation between BMD and SUV in the lumbar spine at baseline ($P < 0.05$), there was no correlation between the 2 variables at 12 mo of treatment with alendronate. **Conclusion:** Alendronate treatment resulted in significant decreases in bone metabolism and turnover in the lumbar spine. It also led to an increase in BMD of the lumbar spine in patients with glucocorticoid-induced osteoporosis. Our findings suggest that antiresorptive therapy has a direct bone-metabolism effect on skeletal kinetics in glucocorticoid-induced osteoporosis at the clinically important site of the lumbar spine.

Key Words: glucocorticoid; osteoporosis; ^{18}F-fluoride positron emission tomography (PET); bone metabolism; alendronate

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The use of glucocorticoids in the treatment of patients with various diseases is associated with increased bone loss and the risk of bone fractures. Glucocorticoid-induced osteoporosis is the result of a combination of systemic effects on mineral metabolism and local effects on bone quality. Glucocorticoids decrease intestinal absorption of calcium and increase renal calcium excretion (*1,2*). Another important effect of glucocorticoids on bone is inhibition of bone formation by a decrease in the number of osteoblasts and hampering of their function (*3*). Glucocorticoids also increase the rate of bone resorption by stimulating the formation and action of osteoclasts. Although a daily dose of 7.5 mg or more of prednisone for at least 6 mo can induce osteoporosis (*4,5*), lower doses of the drug have also been linked to such changes (*6*). Several international guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis have been developed (*7–10*). In general, these guidelines recommend the use of bisphosphonate supplementation, in addition to supplementation with calcium and vitamin D_3, especially in patients at high risk of fractures. Alendronate is effective in preventing and treating glucocorticoid-induced osteoporosis (*11–13*).

Functional imaging with ^{18}F-fluoride PET allows quantitative analysis of bone metabolism in specific skeletal regions (*14*). The preferential rapid uptake of ^{18}F-fluoride

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reflects sites of high osteoblastic activity related to bone remodeling (*15,16*). Furthermore, ^{18}F-fluoride has been used to measure bone blood flow, and a significant correlation was reported between ^{18}F-fluoride uptake and osteoblastic activity, as determined by bone morphometry (*17*). Extension of these studies to regional bone metabolism showed significant relationships between regional skeletal kinetic parameters measured by ^{18}F-fluoride PET (*18*) and the number and activity of osteoblasts, as well as bone formation and mineral apposition rate (*19,20*). The plasma clearance technique used in these studies has also been used clinically to correlate changes in bone metabolism with the type and severity of metabolic bone disease, such as osteoporosis (*21*), renal osteodystrophy (*19*), and Paget disease (*22,23*). However, only a few studies have quantitatively determined bone turnover and metabolism in glucocorticoid-induced osteoporosis by radiologic imaging techniques including PET (*24*). To our knowledge, there is no information on regional changes in bone metabolic activity (e.g., lumbar spine) in patients treated with alendronate for glucocorticoid-induced osteoporosis.

The present prospective study was designed to determine the effects of alendronate treatment on regional bone turnover, measured by ^{18}F-fluoride PET and by global biochemical markers and bone mineral density (BMD), in postmenopausal women with glucocorticoid-induced osteoporosis.

MATERIALS AND METHODS

Subjects

The study population consisted of 24 Japanese postmenopausal women (mean age, 59.7y; range, 50–69 y) free of rheumatoid arthritis, who had been treated with at least 10 mg of oral glucocorticoids (prednisolone equivalent) per day for more than 6 mo. The underlying conditions included systemic lupus erythematosus in 5 patients, pemphigus in 4, pemphigoid in 4, polymyositis or dermatomyositis in 3, asthma in 3, multiple sclerosis in 2, malignant lymphoma in 2, and Behçet disease in 1. None had a history of fractures. Excluding these diseases, none of the patients had any other disease or took any medications, including calcium, that affected bone metabolism before baseline measurements.

Treatment with 5 mg of oral alendronate once daily was initiated on the day after the first ^{18}F-fluoride PET scan and continued for the duration of the study (12 mo). All examinations, including ^{18}F-fluoride PET, strictly followed the Ethics Review Committee Guidelines of Fukui University, and written informed consent was obtained from all patients. The ^{18}F-fluoride PET study was undertaken as an Advanced Medical Technology Development Project at Fukui University.

Measurement of BMD

BMD was measured at the time of study entry (baseline), 6 mo, and 12 mo. BMD of the lumbar spine (L1–L4) in the posteroanterior projection and femoral neck (left side), expressed in g/cm^2, was measured with dual-energy x-ray absorptiometry (QDR 1000; Hologic). In our university, the coefficient of variance at these sites was less than 2%. The BMD scan was performed within 2 wk of the ^{18}F-PET scan and measurement of biochemical markers.

Measurement of Biochemical Markers

Serum bone-specific alkaline phosphate (BSALP), a marker of bone formation, was measured in nonfasting patients at baseline and at 3, 6, and 12 mo. Urinary N-telopeptide for type I collagen (NTx), a marker of bone resorption, was measured in fasting patients (morning, second urine) at baseline and at 3, 6, and 12 mo. Blood and urine specimens were collected on the same day as the PET examination and stored frozen (−20°C) until measurement. BSALP and NTx were measured quantitatively using Metra BAP (Quidel Corp.) and Osteomark NTx (Inverness Medical Innovations), respectively, in a fully automated enzyme immunoassay apparatus (plate enzyme immunoassay multisystem EMS-01; Nippon Advanced Technology), and the serum and urinary values were estimated from the respective optical absorption rate.

^{18}F-Fluoride PET

^{18}F-fluoride PET was performed using the Advance system (GE Healthcare). This system allows simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm, with septa (2-dimensional mode). Performance tests showed that the intrinsic resolution of the scanner was 4.0–5.3 mm in the axial direction and 4.6–5.7 mm in the transaxial direction. The field of view and pixel size of the reconstructed images were 512 and 4 mm, respectively. A dose of 185 MBq of ^{18}F ions was injected into the anterocubital vein over a period of 10 s. Fifty minutes after the tracer injection, the patient was positioned supine in the PET scanner, and an emission scan was started at a rate of 2 min per bed position from the skull to the mid thigh (7–8 bed positions). After the emission scan, postinjection transmission scanning was performed for 1 min per bed position at the same position as for the emission scan, using a standard ^{68}Ge/^{68}Ga rod source for correction of attenuation. The acquired data were reconstructed by an iterative method with selection of 14 subsets and 2 iterations. The reconstructed tissue-activity images were converted into standardized uptake value (SUV) images corrected for the injected dose and patient's body weight using the following equation:

$$\text{SUV} = \text{tissue activity (kBq/mL)} \times \text{body weight (kg)}/\text{injected } ^{18}\text{F ion dose (MBq)}.$$

The images were processed using Dr. View software (AJS Co. Ltd.) on a Linux workstation. With this software and hardware, ^{18}F-fluoride PET images were visualized and conformed into 3-dimensional sections. A region of interest (18 × 18 mm) was placed at the center of each vertebral body from L1 to L5 in the sagittal plane (Fig. 1A) and at the center of the left femoral neck in the coronal plane (Fig. 1B). The mean SUVs of the lumbar vertebrae and femoral neck were plotted as localized bone metabolism parameters against the values of BMD or biochemical markers. ^{18}F-fluoride PET images were obtained at baseline, 3 mo, and 12 mo.

Statistical Analysis

All values were expressed as mean ± SD. The unpaired *t* test was used to compare differences in bone turnover markers between patients with low and high BMD T-scores at baseline. The paired *t* test was used to compare differences in bone turnover markers (BSALP, NTx, and SUV) and BMD between baseline and 3,

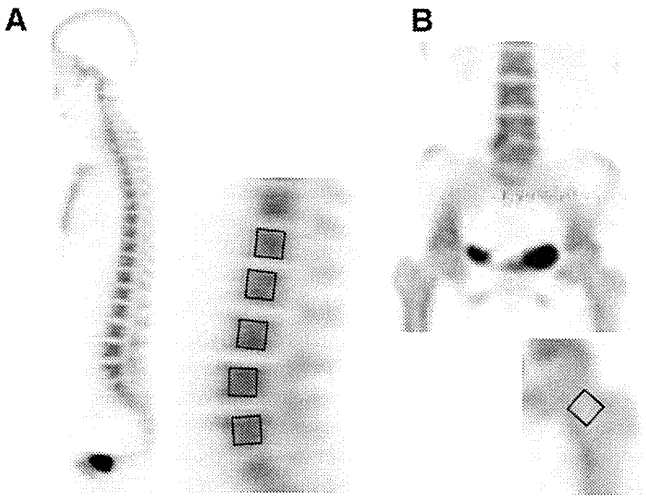

FIGURE 1. (A) Midsagittal ^{18}F-fluoride PET image through lumbar vertebrae showing region of interest within vertebral bodies (at right is magnification of L1–L5 vertebral bodies, with squares indicating regions of interest). (B) Coronal image of pelvis and both proximal femurs (at bottom is magnification of left femoral neck, with square indicating region of interest).

6, or 12 mo of treatment. The correlations between BSALP, NTx, lumbar spine BMD, and lumbar spine SUV at baseline and 12 mo of treatment were examined by Pearson correlation coefficients. A P value of less than 0.05 was considered to represent statistical significance. All statistical analyses were conducted using SPSS software (version 15.0).

RESULTS

Table 1 summarizes the baseline characteristics of the study group. The mean time since menopause was 9.8 y (range, 3–19 y). The mean T-scores of the lumbar spine and the femoral neck were −2.2 (range, −4.43 to −0.16) and −2.9 (range, −4.8 to −0.6), respectively. The mean dose of oral glucocorticoids (prednisolone equivalent) before and during the study was 13.7 ± 2.3 mg/d. The values of both BSALP and NTx showed marked variability among the subjects, and the mean NTx tended to be higher than the normal value in our institution. The SUVs of the lumbar spine and the femoral neck were 5.2 ± 0.72 and 2.5 ± 0.47, respectively, and the former was significantly higher than the latter.

TABLE 1. Baseline Characteristics

Characteristic	Mean	SD	Range
Age (y)	59.7	6.3	50–69
Time since menopause (y)	9.8	6.0	3–19
Weight (kg)	53.0	8.5	40–70
Height (cm)	153.0	4.7	144–164
Prednisolone equivalent (mg/d)	13.7	2.3	11–18
Lumbar spine BMD (g/cm^2)	0.78	0.08	0.56–0.91
Lumbar spine T-score	2.2	0.90	4.43–0.16
Femoral neck BMD (g/cm^2)	0.72	0.09	0.54–0.95
Femoral neck T-score	2.9	0.88	-4.8–0.6
BSALP (U/L)	27.0	11.3	9.6–56.7
NTx (nmol BCE/nmol Cr)	56.5	22.3	20.1–97
Lumbar spine SUV	5.2	0.72	4.23–6.95
Femoral neck SUV	2.5	0.47	1.58–3.35

BCE = bone collagen equivalent; Cr = creatinine.

According to the baseline BMD T-score of the lumbar spine, based on the World Health Organization criteria (*25*) for the diagnosis of osteoporosis, patients were categorized into a healthy/osteopenic group (T-score > −2.5) or an osteoporotic group (T-score ≤ −2.5) (Table 2). The mean values of BSALP, NTx, and femoral neck SUV at baseline tended to be higher in the osteoporotic group, but the differences were not significant. On the other hand, the lumbar spine SUV was significantly lower in the osteoporotic group ($P < 0.05$).

Table 3 shows the serial changes in BSALP, NTx, SUV, BMD, and T-score at 3, 6, and 12 mo of alendronate treatment. Treatment for 12 mo tended to reduce BSALP, NTx, lumbar spine SUV, and femoral neck SUV but gradually increased BMD and the T-score of the lumbar spine and femoral neck, relative to baseline values. Although alendronate treatment over a span of 12 mo significantly increased the level of BMD of the lumbar spine ($P < 0.05$), such treatment significantly reduced BSALP ($P < 0.05$), NTx ($P < 0.01$), and SUV levels of both the lumbar spine ($P < 0.01$) and the femoral neck ($P < 0.01$) during the same period. Figure 2 shows percentage changes in these parameters at 3, 6, and 12 mo. The percentages for BSALP were 76.8% and 73.1% at 6 and 12 mo, respectively ($P < 0.05$), whereas those for NTx were 53.7%, 44.2%, and 40.5% at 3, 6 and 12 mo, respectively ($P < 0.01$). The percentages for lumbar spine SUV were 92.4% and 85.6% at 3 and 12 mo, respectively, and the percentages for femoral neck SUV were 90.4% and 75.7% at 3 and 12 mo, respectively. The percentage changes in lumbar spine SUV were significant at 3 mo ($P < 0.05$) and 12 mo ($P < 0.01$), as was the percentage change in femoral neck SUV at 12 mo ($P < 0.01$). The increase in BMD for the lumbar spine at 12 mo was 8.2%, which was significant relative to baseline ($P < 0.05$).

At 12 mo of alendronate treatment, lumbar spine SUV was decreased in all patients. BSALP decreased in 19 patients (79%) but increased in 5 patients, and NTx decreased in all 24 patients (100%). On the other hand, femoral neck SUV decreased in 20 patients but increased in 4 patients. Of the 20 patients who showed a decrease, 17 (85%) showed a decrease in BSALP and 20 (100%) showed a decrease in NTx. Of the 4 patients who showed an increase in femoral neck SUV, 2 showed a decrease in BSALP and 4 showed a decrease in NTx.

Figure 3 shows the correlations between BSALP, NTx, lumbar spine BMD, and lumbar spine SUV at baseline and at 12 mo of treatment with alendronate. BSALP correlated significantly with SUV at baseline ($P < 0.05$) but not at

TABLE 2. Bone Turnover Markers According to BMD T-Score at Baseline

Marker	T-score > −2.5	T-score ≤ −2.5	P
Number of patients	14	10	–
Lumbar spine BMD (g/cm²)	0.88 (0.14)	0.71 (0.07)	<0.01
Lumbar spine T-score	−1.2 (1.2)	−3.0 (0.59)	<0.01
Femoral neck BMD (g/cm²)	0.77 (0.07)	0.63 (0.06)	<0.01
Femoral neck T-score	−2.4 (0.64)	−3.7 (0.67)	<0.01
BSALP (U/L)	24.2 (9.0)	32.0 (13.7)	0.160
NTx (nmol BCE/nmol Cr)	53.8 (21.8)	56.2 (21.1)	0.802
Lumbar spine SUV	5.9 (1.3)	4.9 (0.46)	<0.05
Femoral neck SUV	2.4 (0.60)	2.6 (0.58)	0.641

BCE = bone collagen equivalent; Cr = creatinine.
Data are mean followed by SD in parentheses.

12 mo. NTx did not correlate significantly with SUV at baseline or at 12 mo. BMD and SUV showed a significant correlation at baseline ($P < 0.05$) but not at 12 mo.

DISCUSSION

The skeletal effects of glucocorticoids are observed mainly in regions with a high content of trabecular bone, particularly the ribs and spine, and seem to depend on the duration and dosage of therapy (*26*). A prednisone dosage exceeding 7.5 mg daily for at least 6 mo is associated with an increased risk of bone loss and fractures (*4,5*), and even lower doses of the drug have also been linked to such changes (*6*). A metaanalysis report of 23 studies indicated that the cumulative glucocorticoid dose was consistent with doses that produced bone loss (*27*); however, the correlation between a specific daily dose or cumulative dose and bone loss or risk of fractures was inconsistent in several individual studies (*26*). Patients in the present study had been treated with oral glucocorticoids at more than 10 mg/d for more than 6 mo but had no history of fractures. Patients were also selected on the basis of not being on any medications, including calcium, that could have affected bone metabolism Because of this strict criterion for this prospective study, and because treatment guidelines in Japan call for treating most osteoporotic patients with bisphosphonate-containing medications at 3 mo after the initiation of glucocorticoids, only 24 patients could be enrolled. The mean BMD of the lumbar spine at baseline (0.78 g/cm²) for our patients was below the cutoff for fracture-prone Japanese individuals (0.82 g/cm²). These individuals represented glucocorticoid-treated osteoarthritic patients free of rheumatoid arthritis who were treated with more than 5.0 mg of glucocorticoids per day (*10*).

Patients with glucocorticoid-induced osteoporosis are reported to have abnormalities in global biochemical markers of bone turnover and metabolism, although the reported changes have been inconsistent (*28,29*). Theoretically, the use of glucocorticoids is associated with reductions in markers of bone metabolism reflecting decreases in bone formation, although markers of bone resorption show inconsistent changes during the same treatment. In a report of a randomized placebo-controlled trial, prednisone rapidly and significantly decreased both markers of bone formation and markers of bone resorption (*30*). In the present study, the mean baseline BSALP of our postmenopausal women was within the reference range; however, the mean baseline NTx tended to be above the reference range though a

TABLE 3. Serial Changes in Bone Turnover Markers and BMD During Treatment with Alendronate

Marker	Baseline	Treatment with alendronate		
		3 mo	6 mo	12 mo
BSALP (U/L)	27.0 (11.3)	22.6 (8.7)	19.7 (9.0)*	18.5 (6.6)*
NTx (nmol BCE/nmol Cr)	56.5 (22.4)	26.2 (8.4)†	22.3 (8.0)†	20.5 (6.2)†
Lumbar spine SUV	5.2 (0.72)	4.8 (0.48)*		4.4 (0.48)†
Femoral neck SUV	2.5 (0.47)	2.2 (0.53)		1.8 (0.51)†
Lumbar spine BMD (g/cm²)	0.78 (0.079)		0.80 (0.076)	0.84 (0.077)*
Lumbar spine T-score	−2.2 (0.90)		−2.0 (0.73)	−1.6 (0.75)*
Femoral neck BMD (g/cm²)	0.72 (0.093)		0.72 (0.090)	0.77 (0.084)
Femoral neck T-score	−2.9 (0.88)		−2.7 (0.85)	−2.3 (0.74)

*$P < 0.05$.
†$P < 0.01$ vs. baseline.
BCE = bone collagen equivalent; Cr = creatinine.
Data are mean followed by SD in parentheses.

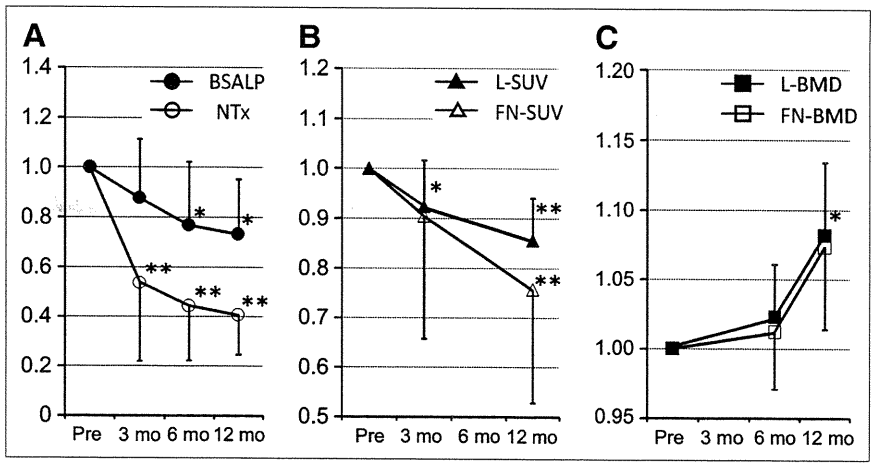

FIGURE 2. Percentage changes in BSALP and NTx (A), SUV of lumbar spine and femoral neck (B), and BMD of lumbar spine and femoral neck (C) after alendronate treatment relative to baseline values. Percentage change in BSALP was significant at 6 and 12 mo; that of NTx was significant at 3, 6, and 12 mo. Percentage change in lumbar spine SUV was significant at 3 and 12 mo; that of femoral neck SUV was significant at 12 mo. Percentage change in BMD of lumbar spine was significantly different only between baseline and 12 mo of treatment. $^{*}P < 0.05$. $^{**}P < 0.01$. FN = femoral neck; L = lumbar spine; Pre = pretreatment.

statistical comparison of our patients and controls without glucocorticoid therapy was not performed. It is possible that certain factors such as age, sex, time since menopause, and background disease may affect the level of bone resorption.

Bisphosphonates induce apoptosis of osteoclasts and inhibit bone resorption (*13,31*). Randomized clinical trials showed that treatment with bisphosphonates prevents corticosteroid-induced bone loss (*32*). Alendronate, a member of the bisphosphonate family, is effective in the prevention and treatment of glucocorticoid-induced osteoporosis (*11–13,32*) and has been reported to prevent bone loss and improve the BMD of lumbar vertebrae by reducing both bone formation and resorption and suppressing bone metabolism (*13*). Similarly, alendronate treatment in the present study significantly reduced the levels of both biochemical markers (bone formation and resorption), and the decrease in urinary NTx (a marker of bone resorption) was significant; the suppression effect was approximately 60% after 12 mo. Furthermore, dual-energy x-ray absorptiometry measurement of the lumbar spine showed that 12 mo of alendronate treatment increased BMD by 8.2%. A previous study in postmenopausal women with osteoporosis indicated that the alendronate-induced change in BMD was primarily due to changes in bone resorption (*33*). Considered together, these results suggest that alendronate treatment prevented further reduction in lumbar BMD by reducing bone resorption.

Several studies have examined the feasibility of ^{18}F-fluoride PET for direct assessment of bone turnover in clinically important skeletal sites such as the lumbar spine. Previous studies of patients having disease with high bone turnover showed a significant relationship between bone turnover and biochemical markers (*19,22*). Brenner et al. (*34*) reported that the SUV of ^{18}F-fluoride PET correlated well with markers of bone metabolism; the net uptake of fluoride into the mineral compartment (K_i) was measured using arterial blood sampling and kinetic analysis. We also obtained similar results with 8 postmenopausal women, who showed a significant correlation between K_i and SUV (data not shown). On the other hand, there are some reports of a significant correlation between K_i and the histomorphometric parameters (*19,20*). It is possible that tubular reabsorption of fluoride is affected by patient hydration, which could theoretically affect SUVs. None of our patients presented with renal dysfunction during the course of this study. Therefore, SUVs were substituted for markers of regional bone turnover or bone metabolism because of the simplicity of data acquisition and calculation. However, further research is required to investigate the relationship between regional SUV and histomorphometric parameters. Previous studies of osteoporosis in postmenopausal women with ^{18}F-fluoride PET indicated that such patients exhibit low regional bone formation activity, a good relation between bone turnover and changes in BMD, and a risedronate-related decrease in levels of global markers of bone formation, compared with untreated groups (*21,35*). Although our osteoporotic patients on glucocorticoid treatment did not show a significant change in BSALP and NTx (used as global markers of bone turnover) as measured at baseline, such treatment significantly reduced lumbar spine SUV in the osteoporotic patients, compared with healthy or osteopenic patients. These findings indicate that the decrease in bone turnover in the lumbar spine measured by SUV reflects the degree of osteoporosis. In this regard, it was reported previously that fluoride clearance relative to bone minerals depends not only on the rate of bone metabolism but also on the area available for tracer clearance (*36*). It is possible that a reduction in bone mass, as is often seen in patients with osteoporosis, also reduces the number of sites available for bone remodeling activity, which could indirectly influence the measured SUV in our study (*22*). Accordingly, further studies involving measurements of PET parameters (such as K_i and SUV) and various bone histomorphometric parameters, particularly in trabecular bones, are necessary to determine the relationships between the measured PET values and the bone surface area and volume of such bones.

Follow-up studies have demonstrated that bone resorption significantly decreases within 1 mo of the commencement of antiresorptive therapy, and consequent to the coupling

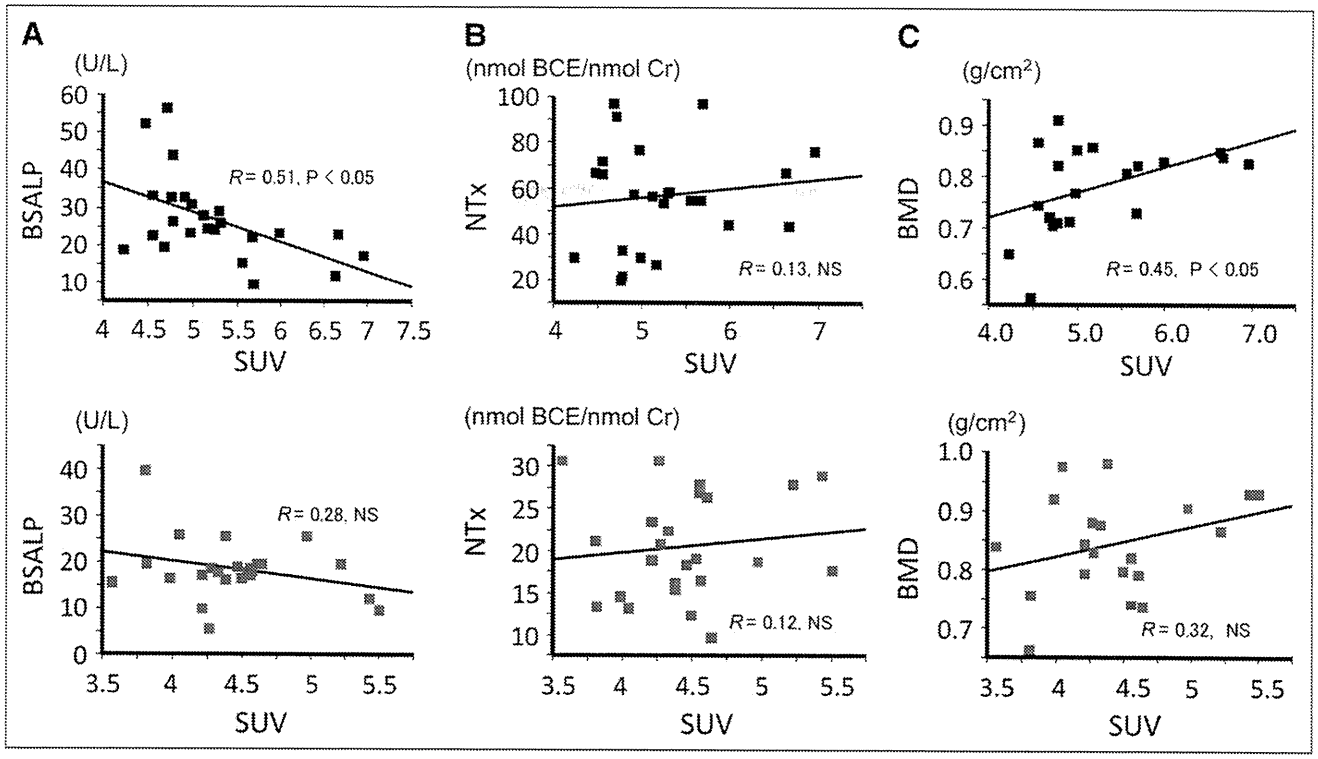

FIGURE 3. Correlations with lumbar spine SUV at baseline (top) and after 12 mo of treatment with alendronate (bottom). (A) BSALP correlated with SUV significantly at baseline ($y = 68.7 - 8.0x$, $R = 0.51$, $n = 24$, $P < 0.05$) but not at 12 mo. (B) No significant correlation was found between NTx and SUV either at baseline or at 12 mo. (C) A positive correlation that was found between BMD and SUV at baseline ($y = 0.5 + 0.05x$, $R = 0.45$, $n = 24$, $P < 0.05$) disappeared after treatment with alendronate for 12 mo. BCE = bone collagen equivalent; Cr = creatinine.

between resorption and formation, a secondary suppression of bone formation occurs within 3 mo (*37*). In a quantitative study of regional bone metabolism using ^{18}F-fluoride PET, K_i decreased significantly after 6 mo of risedronate therapy in postmenopausal women (*38*). In the present prospective study, BSALP and NTx started to decrease within 3–6 mo of alendronate treatment; they had decreased by 27% and 60%, respectively, from baseline at 12 mo of alendronate therapy. These changes in global bone turnover markers were also coupled with similar decreases in SUV in both the lumbar spine and the femoral neck, reflecting regional bone turnover or metabolism, although not similarly so in all patients. Interestingly, there was a significant correlation between BSALP at baseline and the SUV, but not at 12 mo. Changes in NTx at baseline and 12 mo were not significant relative to SUV; for BSALP, the slope of the negative line tended to decrease after treatment, and for NTx, the slope of the positive line tended to decrease after treatment (Figs. 3A and 3B). These results suggest that the rate of decrease of both BSALP and NTx was more than that of regional SUV after alendronate treatment. The decreases in SUV were accompanied by a small but significant increase in lumbar spine BMD at 12 mo after treatment, though no such change was noted for femoral neck BMD. Interestingly, larger studies of antiresorptive therapy tend to report weaker correlations between biochemical markers and changes in BMD for the femoral neck than for the lumbar spine (*39*). On further consideration, our patients with higher baseline regional SUV and biochemical markers did not show the greatest increases in BMD in response to alendronate, although there have been some reports that subjects with higher global bone turnover and suppressive effects of biochemical markers show greater increases in BMD (*40*). It could be that for some reason their regional or global bone turnover at baseline had been influenced by glucocorticoid treatment, background disease, or other factors and tended to be insensitive to alendronate. In general, alendronate exerts a potent inhibitory effect on bone resorption without interfering with bone calcification. Its effect is associated with increased BMD and decreased bone resorption markers, and a secondary decrease in bone formation including osteoblastic activity, thus producing normalization of bone metabolism. Although we cannot ignore the fact that both SUV and BMD could be associated with relatively large measurement errors and that the mechanism of action and potency of alendronate may differ in terms of BMD in each patient, our results indicate that alendronate treatment caused a further decrease in SUV with a subsequent increase in BMD at the same level in the lumbar spine, though it was not significant at 12 mo of treatment, and that SUV and BMD correlate significantly in postmenopausal osteoporotic women on steroid therapy before antiresorptive therapy.

CONCLUSION

To our knowledge, this was the first study of regional bone metabolism in the lumbar spine measured using ^{18}F-fluoride PET in patients with glucocorticoid-induced osteoporosis. The study also examined various bone metabolism markers before and after alendronate treatment. The results demonstrated decreased bone turnover in the lumbar spine, represented by SUVs, and a correlation between these changes and the severity of osteoporosis. Furthermore, the results showed a significant decrease in bone metabolism associated with increased BMD in the lumbar spine after 12 mo of treatment with alendronate. These results suggest that antiresorptive therapy has a direct bone-metabolism effect on skeletal kinetics in glucocorticoid-induced osteoporosis at the clinically important site of the lumbar spine.

ACKNOWLEDGMENTS

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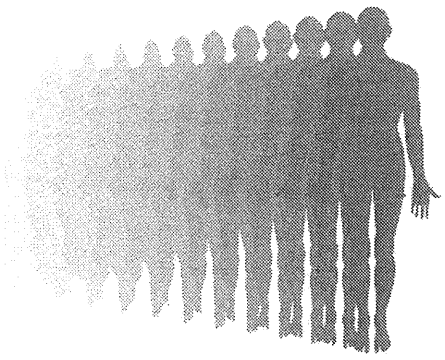
【テーマ①】

痛みの疫学
—国内外の文献から—



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はじめに

痛みは症状であって，疾患名にはならない．しかし慢性疼痛の場合，ある疾患の症状として痛みが表れてはいるのではあるが，何がその原因なのかがわからないことも多い．最近，痛みは，血圧，体温，呼吸，脈拍に次ぐ第5のバイタルサインといわれている．しかし，前者4つは絶対的数値として表すことができるが，痛みはVAS(visual analogue scale)のような評価はあっても，絶対的な数値では表現できず，他者との比較もできないため，あくまでも個人内評価しかできない．このような背景からもわかるように，疼痛の疫学調査ははなはだ困難である．さらに単純に比較できない理由として，医療制度，生活習慣や文化的背景の違いも無視できない要素であるからである．

本稿において，痛みのなかでも特に慢性疼痛の発生頻度について，これまでの国内や海外からの報告について紹介する．

利用文献

本邦での発生頻度は国内論文および厚生労働省発表の統計データを引用した．海外は欧米を中心とした論文から引用した．特に筋骨格筋系の疫学調査を中心として発生頻度を検討した．慢性疼痛の定義については明らかな規定がないため，今回は「一定期間以上続く痛みが存在し，そのために身体的，社会的に大きな影響を及ぼすもの」と定義して論文検索を行った．

結　果

1．日本

本邦において，筋骨格系および結合組織の疾患患者は，厚生労働省の発表によると毎日約100万人が医療機関を受診しており，毎年約1兆8400億円が費やされている(表1)[1,2]．筋骨格筋疾患患者のなかには骨折・脱臼など急性外傷患者も含まれているが，多くは慢性疼痛患者が占められていると考えられる．慢性疼痛患者に対して，多くの医療資源が費やされているにもかかわらず，本邦における慢性疼痛に関する疫学の報告が少ない．慢性疼痛全体の保有率の報告は，検索し得た範囲では服部らの論文のみであった[3]．それによると慢性疼痛の発生頻度は13.4%であり1700万人の日本国民が患っていることになる．その発生頻度は年齢とともに上昇しており，30歳までは男女差はないが，30歳以上では女性の発生頻度は男性よりも上昇していた．平成19年国民生活基礎調査[4]では症状

表1　筋骨格系および結合組織の疾患

推計外来患者数 －平成20年患者調査－	受療率 －平成20年患者調査－	医療費薬剤等含む －平成19年国民医療費－
94.5万人 （1日あたりの受診者）	740 （人口10万人対）	18,433 （億円）

（文献1，2より引用）

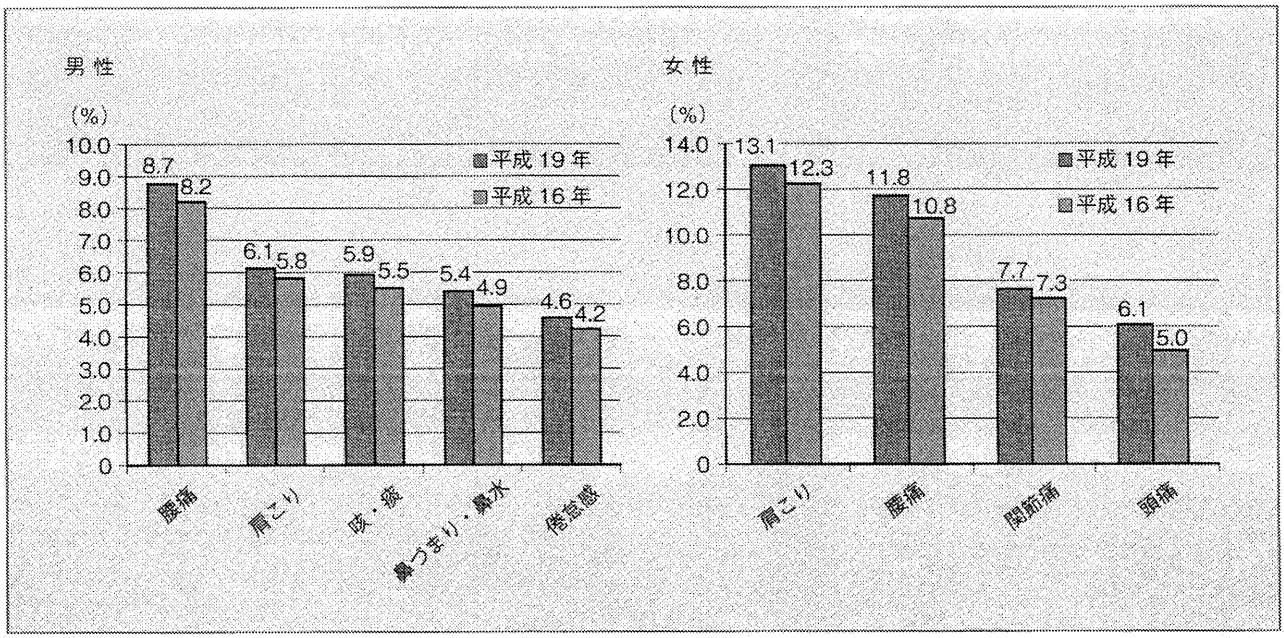

図1　自覚症状の割合

（文献4より引用）

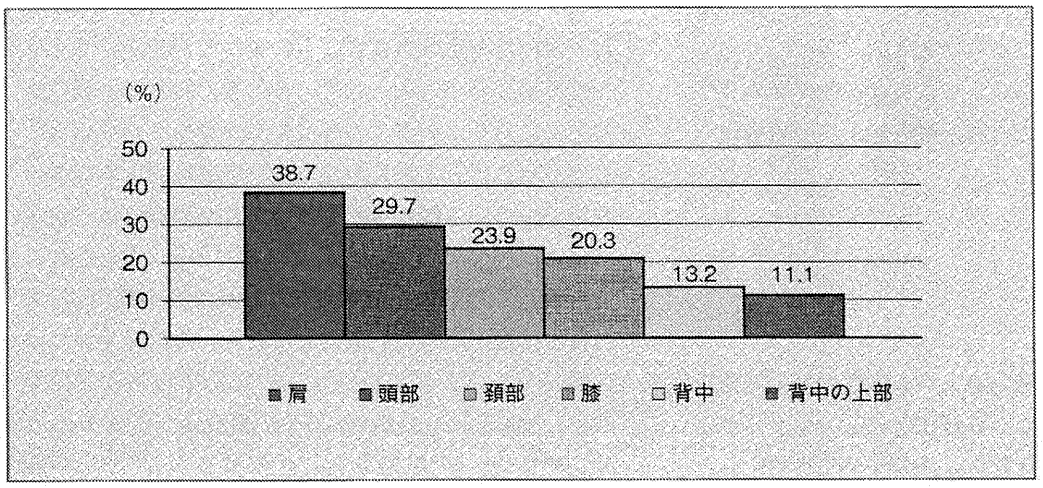

図2　慢性疼痛の部位

（文献3より引用）

表2　年齢別自覚症状の発生頻度（平成19年人口1000人あたり）

症状	総数	0～4歳	5～9	10～14	15～19	20～24	25～29	30～34	35～39	40～44	45～49
有訴者率	327.6	271.5	211.8	201.4	205.2	208.9	239.3	267.2	280.3	292.9	298.2
頭痛	44.4	2.7	10.9	25.7	39.3	44.2	56.3	60.5	64.3	62.7	56.3
前胸部に痛みがある	11.3	0	1.1	2.7	5.4	6	6.6	8.3	8.5	9.2	8.8
歯が痛い	21.8	4.5	14.7	9.9	13.9	21.1	20.6	22.6	20.6	21.2	19.8
肩こり	97.1	0.4	1.6	11.2	33.3	60.4	80.9	97.9	107.5	119.1	123.4
腰痛	103.2	0.2	0.9	9.9	30.9	46.8	61.7	77.4	88.6	97.7	103.1
手足の関節が痛む	60.9	0.8	3.5	14.2	12.9	11.5	14.5	17.2	24	37.2	47.9
手足の動きが悪い	29.1	0.5	0.7	1.5	2.7	2.7	3.5	4.6	5.4	8.7	12.1
手足のしびれ	38.7	0.1	0.3	1.3	4.7	6.8	8.5	12.7	17.4	25.8	33.4
足のむくみやだるさ	32	0.1	0.3	2.6	7.5	19.5	22.8	23	25.4	30.4	32.2

全体の有訴者は32.8%

別調査が行われており，主な疼痛は男性では腰痛が8.7%，肩こり6.1%であり，女性では肩こりが13.1%，腰痛が11.8%，関節痛が7.7%であった（図1）．年齢別では乳幼児の保有率が最も低く，年齢とともに疼痛の保有率が増加していた（表2）．有訴者の部位別では肩が38.7%，頭部が29.7%，頚部が23.9%，膝が20.3%，背中が13.2%，背中の上部が11.1%であった（図2）．東京および和歌山での膝関節部痛の疫学調査[5]が行われており，それによると，40歳以上のX線所見上の変形性膝関節症は2530万人，そのうち痛みがあるもの780万人（男性220万人，女性560万人），X線所見上の変形性腰椎症は3790万人，そのうち痛みがあるもの1100万人（男性470万人，女性630万人）であった．

2. 海外

欧州には統一プロトコールで疼痛の疫学調査を行っている「Pain in Europe」という組織がある[6,7]．これは，慢性疼痛の発生率と患者数の推計，慢性疼痛の原因の評価，QOLに及ぼす影響や治療に対する満足度などについて共通の項目で調査し，欧州の46,395人のインタビューデータが蓄積されている．この組織による発表では欧州全体の慢性疼痛患者は19%であり，うち中等度13%，高度が6%と報告している．国別ではノルウェーが最も多く30%，ポーランドは27%，イタリア26%，ベルギー23%，オーストリア21%，フィンランド19%，スウェーデン18%，オランダ18%，ドイツ17%，イスラエル17%，デンマーク16%，スイス16%，フランス15%，アイルランド13%，イギリス13%，スペインが11%と最も少なかった（図3）．

わが国で最も頻度の高い愁訴である肩，腰の疼痛に関しての発生頻度について確認できた文献について表3，4に要約した．成人の肩関節痛の発生頻度は，統計手法に違いがあるためか，フィリピンの2%からイ

	50~54	55~59	60~64	65~69	70~74	75~79	80~84	85歳以上	65歳以上(再掲)	70歳以上(再掲)	75歳以上(再掲)
	321.6	350.7	393.4	439.8	490.2	532.7	556	526.3	496	520.4	538.3
	50.4	42.4	39.6	42.2	44.4	43.6	42.9	38.8	42.8	43.1	42.3
	10.1	12.9	16.3	18.5	24.5	24.8	25.5	24.3	22.9	24.8	24.9
	23.2	23.8	27.5	32.5	31.8	29.6	24.4	20.6	29.5	28.1	25.9
	132.3	130	131.5	133	147.1	137.7	125.2	89.2	132.2	131.8	122.8
	116	124.3	139.7	163	198.2	228.7	228.8	195.6	197.6	212.6	221.2
	65.9	76.7	91	117.6	143.1	170	182.3	169.9	148.8	162.4	173.7
	20.5	26.2	31.4	49.3	74.6	108.9	149.1	182.2	94.7	114.4	137.9
	46.7	54.2	61.5	72.9	90.4	99	109.7	99.2	90.3	97.9	102.3
	34.4	33.5	36.2	44.3	59.6	71	85.3	104.7	65.3	74.4	83.1

(文献4より引用)

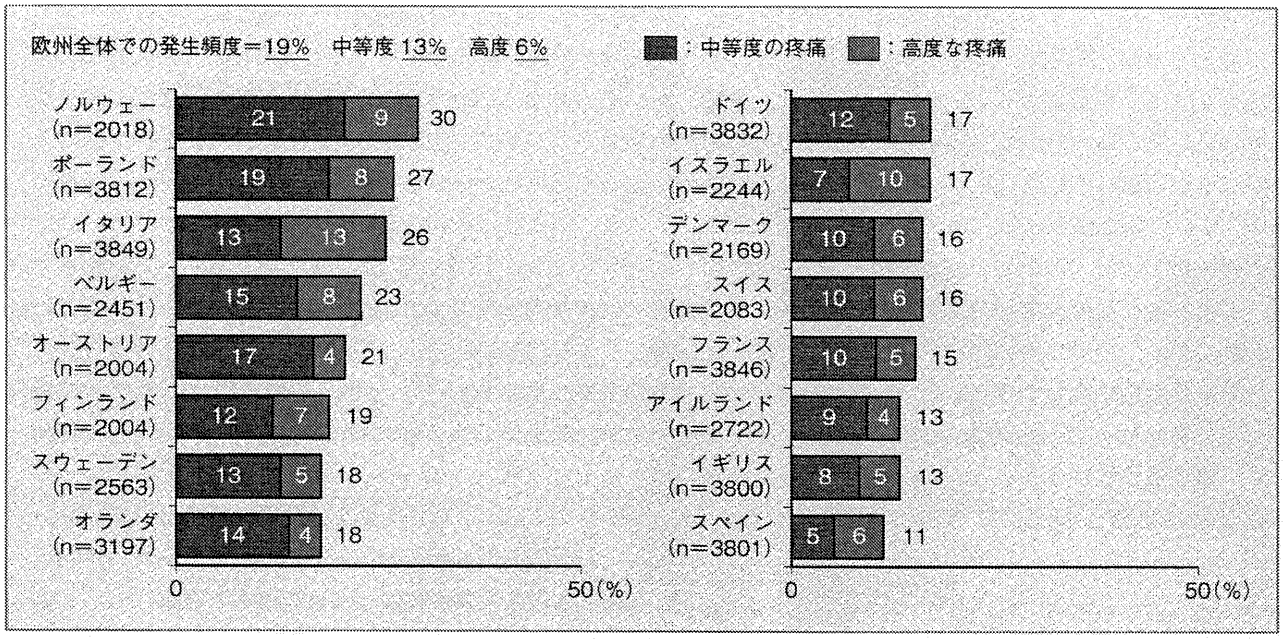

図3　欧州での慢性疼痛の頻度(n＝46,395)

(文献6より引用)

表3　腰痛の発生頻度

文献	地域	調査数	性別	対象年齢(歳)	疼痛期間	発生頻度(%)
8	フィンランド	1045	男	40～64	1年以内にしばしば発生した疼痛	17
		1223	女	40～64		17
9	アメリカ	6913	男女	25～74	過去1カ月間にほぼ毎日	7
10	スウェーデン	319	男	55	過去1カ月間に1日以上	13
		255	女	55		15
11	スウェーデン	827	男女	18～84	6カ月以上	23
12	スウェーデン	917	男	25～74	3カ月以上	18
		889	女	25～74		22
13	イギリス	312	男女	18～75	過去1カ月間に1日以上	34
14	イギリス	6000	男女	18～75	過去1カ月間に1週間以上	16
15	フィリピン	482	男	>15	調査時	2
		468	女	>15		3
16	イギリス	644	男女	>70	調査時	26

ギリスの34%までと大きな開きがみられたが，男女による発生頻度の差はみられなかった(表3)．成人の腰痛発生頻度は，問診時に症状がある割合は13～28%であった．1年以内の腰痛歴は36～67%と大きな開きがみられた．また，腰痛の既往歴は58～84%であった(表4)．

考　察

本邦では，慢性疼痛のなかでも筋骨格系および結合組織の疾患患者は非常に多く，その疾病のためにQOLに大きな影響を与えている．しかし，そのような患者に関した実態調査研究は少なく，多くの人々の痛みからの解放を目指した医療の質向上のためには，基礎的疫学資料が必要である．

わが国の慢性疼痛は欧米と比較するとその発生頻度は低いほうに該当する．ただ，疼痛に関する疫学調査が行われている国は，欧米が中心であり，アジアを含む発展途上国の論文はきわめて少なかった．そのため，本邦における慢性疼痛の頻度が少ないのは，医療事情によるものか，人種差によるものかはわからなかった．今後本誌の発刊により，日本を含むアジア地域での慢性疼痛に対する疫学調査・病態研究・治療研究が発展

表1 腰痛の発生頻度

文献	地域	調査数	性別	年齢(歳)	問診時腰痛率(%)	腰痛罹患率		腰痛既往率(%)
						疼痛期間	頻度(%)	
17	スウェーデン	716	男	40~47	—	過去1カ月間	31	61
18	スウェーデン	1640	女	38~64	—	過去1カ月間	35	67
19	イギリス	2667	男	20~59	—	1年以内に1日以上	36	58
20	イギリス	6106	男女	>18	14	1年以内に1日以上	37	—
21	イギリス	1884	男	18~75	—	過去1カ月間に1日以上	35	59
		2617	女	18~75	—		42	59
22	イギリス	3184	男女	25~64	19	1年以内に1日以上	39	59
23	ベルギー	4208	男女	15	19	—	—	59
24	デンマーク	1370	男女	30~50	—	過去1年間	52	64
25	カナダ	2184	男女	20~69	28	—	—	84
26	スペイン	2998	男女	>20	15	—	—	—
27	オーストラリア	1913	男女	>18	26	過去1年間	67	79
28	ノルウェー	1158	男女	17~67	13	過去1年間	41	61

することを期待する.

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シンポジウム SYMPOSIUM

■四肢のしびれ感

圧迫性頚髄症の痛みとしびれ

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Pain and Numbness in Cervical Stenotic Myelopathy

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Key words：しびれ(numbness)，痛み(pain)，後縦靱帯骨化症(ossification of posterior longitudinal ligament)，頚椎症性脊髄症(cervical spondylotic myelopathy)，患者報告アウトカム(patient reported outcome)

多施設横断研究により圧迫性脊髄症の痛み・しびれに関する調査を行った．後縦靱帯骨化症と頚椎症性脊髄症288名と健常者に患者背景，画像とともにquality of life(QOL)・頚椎関連・心理ストレス・痛みとしびれを調査した．治療内容によらず健常者に比しすべてのアウトカムが低下していた．活動制限を生じる痛みが保存治療で10%，手術治療で15%にみられた．痛みは腰・頚部，しびれは四肢が強く，numerical rating scale(NRS)5以上の頚部痛が36%，上肢しびれが41%にみられた．上肢しびれは四肢・体幹機能や心理ストレスと関連があり，満足度と相関していた．

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はじめに

脊椎外科医は圧迫性脊髄症に対して麻痺の改善を第一の治療目標としてきた．ところが手術後も脊椎の痛みや四肢のしびれがしばしば残存し，麻痺の改善にもかかわらず痛み・しびれを強く訴える患者に遭遇する．しかし過去の研究は運動障害とその回復に関心が寄せられてきたため，こうした痛み・しびれに対して焦点を当てた研究は多くはない．本研究の目的は圧迫性脊髄症患者の実態を把握し，痛み・しびれの患者へのインパクトを解析することである

対象・方法

本研究は厚生労働省難治克服事業脊柱靱帯骨化症の多施設研究として21の大学病院とその関連施設で行われた．調査期間は2006年7月から2007年11月である．対象は頚椎後縦靱帯骨化症(OPLL)と頚椎症性脊髄症(CSM)で，保存治療・手術治療ならびに対照として調査した健常者の計3群を比較した．

調査内容は患者背景と疾患・治療内容，画像情報，患者報告アウトカムの3つである．

患者背景として年齢・性別・感覚障害出現から現在(あるいは手術)までの期間・運動障害出現から現在(あるいは手術)までの期間，手術症例では手術アプローチを，画像情報としてX線像での脊柱管前後径，MRIでのT2高輝度の有無と頭尾側方向の長さである．患者アウトカムとして，

1) 包括的調査票としてSF-8[3]の8つのドメイン，
2) 頚椎症あるいは頚髄症調査票として日本整形外科学会頚部脊髄症治療成績判定基準JOACMEQ[4]，医師評価である日本整形外科学会頚椎疾患治療成績判定基準(旧JOAスコア)，頚椎症尺度であるneck disability index(NDI)[5]を，
3) 脊柱の可とう性評価として作成し前屈時指床距離(finger floor distance)と相関のあるself-assessment bending scale(SABS)[1]を，
4) 心理評価として日本語POMS短縮版(profile of mood states)[8]を用いた．30の質問からなり，緊張・抑うつ・怒り・活気・疲労・混乱の6因子が同時に測定できる質問票である．

痛みとしびれの評価としては，痛み評価ではchronic pain grade(CPG)と，身体部位別(頚部・頭部・背部・上肢・腰部・下肢の6つ)の11段階による痛みおよびしびれ強度(numerical rating scale : NRS)を調査した．CPGはグレート0から4まであり，高いほど障害が強い．またCPGの質問票から疼痛強度も算出し比較した．

さらに，上肢しびれに関連する因子の検索と，満足度との関連を解析した．

結果

1．アウトカム

調査総数は350名で，内訳はOPLLの保存治療80名，OPLLの手術治療104名，CSMの保存治療53名，CSMの手術治療69名，健常者44名であった．保存治療，手術治療，健常者の特徴を表1に示す．保存治療，手術治療いずれも男性に多く，平均年齢は60歳代であった．手術治療は前方29例，後方138例，その他6例であった．脊柱管前後径は差がなかったが，保存治療群ではMRIのT2高輝度のない症例が多かった．

1) 患者報告アウトカム

SF-8では健常者に比べて保存治療，手術治療ともすべてのドメイン，特に身体機能が低かった(表2)．保存治療，手術治療に有意な差はなかった．JOACMEQでも健常者に比べてすべてのドメインで保存治療，手術治療とも低かったが，頚椎機能は手術治療群が一段と低かった(表2)．旧JOAスコアでは感覚スコアで上肢と体幹で有意差があるものの，保存治療と手術治療の差はほとんどなかった(表3)．NDIでは保存治療群で29.3±17.5，手術治療群で29.8±18.5で同等であったが，健常者5.6±7.5に比べ有意に高かった($p=0.000$)．

SABS(高値ほどやわらかい)でみる体幹のやわ