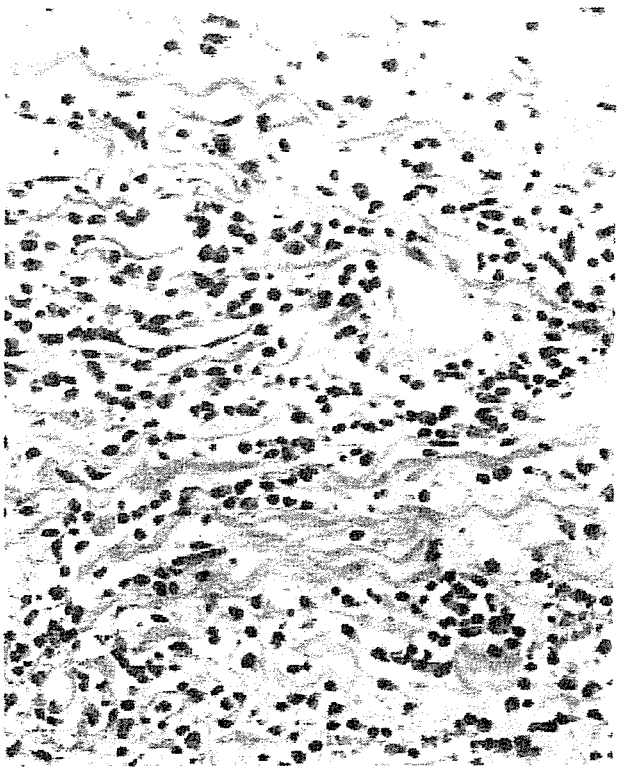

FIG. 2. Photomicrograph of a section of the excised dura mater, showing plasma cells and infiltrating lymphocytes. Whether the arachnoid mater was infiltrated is unclear. H & E, original magnification × 400.

[14,19,22–25] Mikawa and coauthors[17] identified 52 cases in their review of the English- and Japanese-language literature; however, none of the published studies focused on the recurrence of HSP or its possible causes, and few authors reported the long-term course of the disease. To our knowledge, the present article is the first to address specifically the recurrence of HSP.

Park and associates[21] reported that the presence of a residual mass after surgery to treat a ventral lesion of the dura mater. Juhasz[12] found that the inflammatory process did not have definite limits in the caudal and cranial directions and that the inflammation frequently extended to the internal surface of the dura. Based on these observations, it has been proposed that residual inflammation from the irremovable ventral part of the dural lesion leads to recurrence. To test this hypothesis, we searched the PubMed and Cochrane Library databases for reports of cases of HSP by using "hypertrophica," "pachymeningitis," and "recurrence" as search terms. We identified 96 cases (46 of which were described in English and 50 in Japanese), including the two in the present study. Eleven (11%) of the 96 cases involved recurrence (six cases with one recurrence and five with two; Table 1).[1,9,12,13,15–18]

We initially divided the HSP cases into two groups based on recurrence, a nonrecurrence group (85 cases) and a recurrence group (11 cases), and compared them. In the recurrence group, the mean period from the first conservative therapy or surgery to the first recurrence was 1.3 years (range 1 week–4 years). In five of these cases, the lesion recurred twice, and the average time between the first and second recurrence in this subset was 11.3 months (range 3 months–2 years). A two-tailed t-test revealed no significant intergroup difference, except for the duration of the mean follow-up period (Table 2).

We then performed three subgroup analyses. For the first subgroup analysis, we divided the cases into two groups based on the presence or absence of inflammatory signs: 1) a noninflammatory group, which comprised those patients in whom inflammatory signs, including fever, increased erythrocyte sedimentation rate, leukocytosis, and increased C-reactive protein level, were absent before surgery; and 2) an inflammatory group, which comprised those patients who had at least one inflammatory sign. Cases in which there was no mention of inflammation were excluded from this second analysis. The noninflammatory group included a total of 54 cases of HSP, of which two were recurrent. The inflammatory group included a total of 30 cases, of which six were recurrent. A chi-square analysis revealed a statistically significant intergroup difference ($p < 0.05$; Fig. 4).

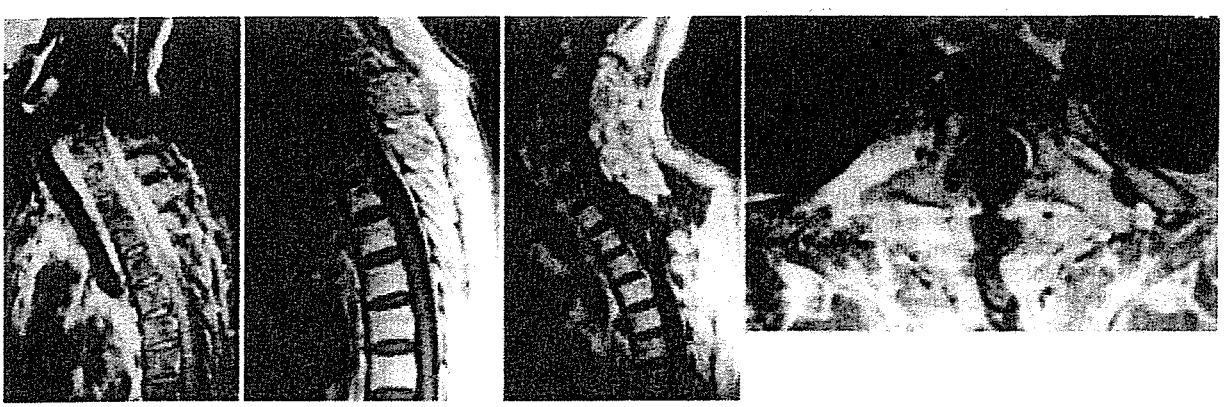

FIG. 3. Case 2. Magnetic resonance images. A: Sagittal Gd-enhanced sequence, revealing HSP at the T1–5 level in the dorsal and ventral dura mater. B: Sagittal Gd-enhanced sequence, showing the same HSP lesion after steroid therapy. C: Sagittal Gd-enhanced sequence obtained after surgery, showing that virtually all of the thickened dura had been removed. D: Axial Gd-enhanced sequence obtained after surgery, demonstrating no dural thickening.

TABLE 1

*Characteristics of 11 patients with recurrent HSP**

Authors & Year	Age (yrs), Sex	Involved Level	Ventral Lesion	Op†	Duration‡	Outcome	FU (yrs)
Juhasz, 1950	16, F	T7–8	—	laminectomy			
1st recurrence		T7–8	—	laminectomy	6 mos	recovered	2.4
Guidetti & La Torre, 1967	15, M	T6–9	—	durotomy			
1st recurrence		C4–T3	—	durotomy	3 yrs	recovered	14
Guidetti & La Torre, 1967	65, F	T4–6	—	durotomy			
1st recurrence		T4–6	—	NST	4 yrs	—	4
Adler, et al., 1991	47, M	T8–11	—	laminectomy			
1st recurrence		C2–7	yes	laminectomy	4 yrs		
2nd recurrence		T1–7	—	laminectomy	2.5 mos	recovered	7
Mikawa, et al., 1994	58, F	T1–11	yes	laminectomy			
1st recurrence		C-7	yes	durotomy	2 wks		
2nd recurrence		C3–6	yes	durotomy	3 mos	recovered	0.5
Kanamori, et al., 1997	28, M	T5–L2	yes	laminectomy			
1st recurrence		T2–?	—	NST	4 mos	recovered	4.2
Mihara, et al., 1997	54, F	T10–12	yes	dura incision			
1st recurrence		T-9	yes	dura incision	1 wk		
2nd recurrence		T-9	yes	durotomy	3 mos	unchanged	0.6
Nagashima, 2001	53, F	C7–T1	yes	laminectomy			
1st recurrence		C7–T7	yes	dura incision	2 mos		
2nd recurrence		T1–8	yes	NST	1 yr, 10 mos	died	2.6
Khadilkar, et al., 2003	42, F	C1–4	yes	durotomy			
1st recurrence		C2–4	yes	NST	1 yr, 3 mos	recovered	5
present study							
Case1	67, M	T6–8	yes	durotomy			
1st recurrence		T3–5	yes	durotomy	3 yrs, 6 mos		
2nd recurrence		C4–T2	yes	durotomy	2 yrs	recovered	10
Case 2	62, M	T1–5	yes	ST			
1st recurrence		C6–T5	yes	durotomy	5 mos	recovered	3

* FU = follow up; NST = nonsurgical treatment; ST = steroid therapy; — = not known.
† Surgery was performed using various methods: laminectomy only, dura incision only, and durotomy with artificial dura mater or fascia.
‡ Duration indicates the time from therapy to recurrence.

For the next subgroup analysis, we compared the cases in which patients underwent durotomy or duraplasty and those in which patients underwent laminectomy alone or only incision, not removal, of the dura mater. The former group included 37 cases of HSP, eight of which were recurrent. The latter group consisted of 41 cases, eight of which were recurrent. The difference was not statistically significant.

For our final subgroup analysis, we divided the cases into those in which both ventral and dorsal inflammation or hypertrophy of the dura mater was documented on pathological, myelography, or MR imaging examination, and those in which only dorsal inflammation or hypertrophy was documented. The former group included 25 cases, eight of which were recurrent. The latter group included five cases, none of which was recurrent. The difference was not statistically significant.

From these results, we concluded that recurrence was not caused by a residual lesion but by active inflammation of the dura mater that was already present before surgery. We considered the possible role of arachnoiditis as an additional cause of recurrence. Friedman and Flanders[8] reported that the peripheral margin in a case of pachymeningitis was enhanced on MR imaging and was unusually close to the highly vascularized arachnoid mater. Oohishi and associates[20] found that this disease process was not just confined to the dura, but also involved the arachnoid mater and pia mater (trimeningitis). Juhasz[12] suggested that HSP associated with arachnoiditis is separate from the arachnoid mater, because the lateral aspect of the dura was found to be relatively intact. Considering that inflammation is often found in the arachnoid as well as the dura, residual arachnoiditis above or below the resected area of the dura mater might cause recurrence, even if the visibly hypertrophic part of the dura is removed. Patients were treated with steroid therapy in 13 cases, some

TABLE 2

*Characteristics and outcome data for 96 cases of HSP with and without recurrence**

Variable	Recurrence	No recurrence
no. of cases	11	85
mean age (yrs)†	46.1 ± 18.8	48.7 ± 15.9
sex (no. of patients)		
Male	5	48
Female	6	37
mean no. of levels involved (range)	3.9 (2–10)	4.2 (1–24)
mean dura thickness (mm) (range)	4.8 (2–8)	6.6 (1–20)
outcome (no. of patients)		
recovered	9	55
unchanged	1	11
died	1	16
unknown	0	3
FU period	4.8 ± 4.1	1.4 ± 2.6

* The difference between groups was significant only for the duration of the average follow-up period ($p < 0.0005$).
† Values are given as means ± standard deviation.

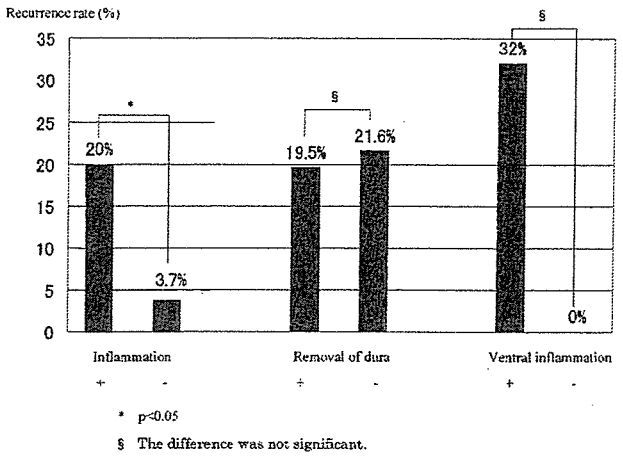

FIG. 4. Bar graph depicting the results of analyses of HSP recurrence rates. Cases with sufficient data were included in the following subgroup comparative analyses: 1) presence or lack of at least one positive inflammatory sign; 2) removal or retention of dura; and 3) presence or lack of ventral inflammation of the dura mater. See *Discussion* for the numbers of patients in each group.

of which, including ours, were recurrent,[1,6,11,13,15,17,18,22] but many of the authors who reported treating patients with steroid agents claimed that the effect was not certain. Hatano and coworkers[10] found that patients with a linear pattern of dural enhancement responded better to corticosteroid therapy than those with a nodular pattern of enhancement. As a result of our analyses of the available data, we conclude that surgical decompression by laminectomy or durotomy and duraplasty is to be recommended for this disease.

Guidetti and La Torre[9] have suggested that removal of the posterior surface of the dura mater beyond the apparent limits of the lesion might be useful in controlling recurrence. In conclusion, we consider that recurrence occurs due to active dural inflammation present before surgery and the influence of chronic inflammation, including residual arachnoiditis.

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Minodronate Suppresses Prostaglandin F2α-induced Vascular Endothelial Growth Factor Synthesis in Osteoblasts

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Abstract

In our previous study, we showed that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) stimulates vascular endothelial growth factor (VEGF) synthesis via activation of p44/p42 mitogen-activated protein (MAP) kinase via protein kinase C (PKC) in osteoblast-like MC3T3-E1 cells. In addition, we demonstrated that incadronate amplified, and tiludronate suppressed $PGF_{2\alpha}$-induced VEGF synthesis among bisphosphonates, while alendronate or etidronate had no effect. In the present study, we investigated the effects of minodronate, a newly developed bisphosphonate, on $PGF_{2\alpha}$-induced VEGF synthesis in MC3T3-E1 cells. Minodronate significantly reduced VEGF synthesis induced by $PGF_{2\alpha}$ dose-dependently at levels between 3 and 100 μM. $PGF_{2\alpha}$-stimulated phosphorylation of Raf-1, MEK1/2 and p44/p42 MAP kinase were suppressed by minodronate. 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a direct activator VEGF synthesis induced by PKC, was inhibited by minodronate. Minodronate inhibited Raf-1, MEK1/2 and p44/p42 MAP kinase phosphorylation induced by TPA. Mevalonate failed to affect the suppressive effect of minodronate on $PGF_{2\alpha}$-induced VEGF synthesis. Taken together, these results indicate that minodronate suppresses $PGF_{2\alpha}$-stimulated VEGF synthesis at the point between PKC and Raf-1 in osteoblasts.

Key Words
Bisphosphonate · prostaglandin $F_{2\alpha}$ · vascular endothelial growth factor · osteoblast

Introduction

Osteoblasts and osteoclasts are main functional cells that regulate bone metabolism. The former is responsible for bone formation, and the latter for bone resorption [1]. Bone-remodeling results from this finely coordinated process of bone resorption by activated osteoclasts coupled with subsequent deposition of new matrix by osteoblasts. Several bone-resorptive agents such as parathyroid hormone and 1,25-$(OH)_2$ vitamin D_3 upregulate RANKL (receptor activator of nuclear factor κB ligand) expression by binding specific receptors on osteoblasts, suggesting that osteoblasts also play crucial roles in the regulation of bone resorption [2]. During these processes, capillary endothelial cells along with microvasculature with osteoblasts and osteoprogenitor cells, which locally proliferate and differentiate into osteoblasts, migrate into the resorption lacuna. Therefore, osteoblasts, osteoclasts and capillary endothelial cells cooperatively regulate bone metabolism in a closely coordinated fashion via humoral factors as well as by direct cell-to-cell contact [3].

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Bisphosphonate, a stable analogue of pyrophosphate, is generally known as an inhibitor of bone resorption [4]. Bisphosphonates are widely used as a potent agent for the treatment of various metabolic bone diseases associated with increased osteoclastic bone resorption such as Paget's disease, tumoral bone disease, and osteoporosis [4]. Osteoclast recruitment, osteoclastic adhesion to bone surface and osteoclast activity inhibition is known to be the main mechanisms by which bisphosphonates inhibit bone resorptive actions [4]. In addition to osteoclasts, the inhibitory action of bisphosphonates on osteoclasts is reportedly partly mediated through its actions on osteoblasts [5,6]. In osteoblastic cell line CRP 10/30, both ibandronate and alendronate induce the synthesis of an osteoclastic bone resorption inhibitor [7]. In a previous study [8], we reported that tiludronate inhibits interleukin (IL)-6 synthesis in osteoblast-like MC3T3-E1 cells. Etidronate, alendronate, pamidronate and olpadronate prevent apoptosis of murine primary cultured osteoblasts via activation of p44/p42 mitogen-activated protein (MAP) kinase [9]. In cultured human fetal osteoblasts, pamidronate and zoledronate enhance differentiation and bone-forming activities [10]. Pamidronate and zoledronate also reportedly increase mRNA expression for osteoprotegerin in primary human osteoblasts [11]. In UMR-106-01 osteosarcoma cells, pamidronate and clodronate decrease receptor activator of nuclear factor κB ligand (RANKL) [12]. In addition, zoledronate upregulates osteocalcin and bone morphogenetic protein-2 (BMP-2) gene expression in human osteoblast-like cells [13], and decreases membrane RANKL expression by upregulating tumor necrosis factor-α-converting enzyme [14]. These studies led us to speculate that the effects of bisphosphonates on bone metabolism are not only exerted by osteoclasts, but also by osteoblasts. However, the detailed mechanism of bisphosphonate action on osteoblasts has not yet been fully clarified.

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that induces angiogenesis, endothelial cell proliferation and capillary permeability [15]. Inactivation of VEGF results in the complete suppression of vascular invasion followed by impaired trabecular bone formation and expansion of the hypertrophic chondrocyte zone in the mouse tibial epiphyseal growth plate [16]. Osteoblasts have been reported to produce and secrete VEGF in response to various physiological agonists [15,17]. In our previous studies, we reported that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a potent bone resorptive agent, activates both phosphoinositide (PI)-hydrolyzing phospholipase C (PI-phospholipase C) and phosphatidylcholine (PC)-hydrolyzing phospholipase D (PC-phospholipase D) [18,19], recognized as two major physiological protein kinase C (PKC) activation pathways [20,21], in osteoblast-like MC3T3-E1 cells. In addition, we recently showed that $PGF_{2\alpha}$ induces VEGF synthesis and secretion through PKC-dependent activation of p44/p42 MAP kinase in these cells [22]. Furthermore, we have demonstrated that incadronate enhances [22], while tiludronate suppresses [23] $PGF_{2\alpha}$-induced VEGF synthesis through activation [22] or suppression [23] of p44/p42 MAP kinase in osteoblast-like MC3T3-E1 cells, while alendronate or etidronate has little effect [22].

In the present study, we investigated the effect of minodronate, a newly developed nitrogen-containing bisphosphonate, which is structurally different and has a different side chain structure from incadronate, alendronate tiludronate or etidronate, on $PGF_{2\alpha}$-stimulated VEGF synthesis in MC3T3-E1 cells and the mechanism behind it. In contrast to the results from incadronate [22], and identical to those from tiludronate [22], this study will demonstrate that minodronate inhibits $PGF_{2\alpha}$-stimulated VEGF synthesis in these cells, and that the suppressive effect of minodronate is exerted at the point between PKC and Raf-1.

Materials and Methods

Materials

Minodronate was kindly provided by Yamanouchi Pharmaceuticals Co. Ltd. (Tokyo, Japan). $PGF_{2\alpha}$, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and mevalonate were purchased from Sigma Chemical Co. (St. Louis, MO). Phosphospecific p44/p42 MAP kinase antibodies, p44/p42 MAP kinase antibodies, phosphospecific MEK1/2 antibodies, MEK1/2 antibodies, phosphospecific Raf-1 antibodies and β-actin antibodies were purchased from New England Biolabs, Inc. (Beverly, MA). ECL Western blotting detection system was purchased from Amersham Japan (Tokyo, Japan). Mouse VEGF ELISA kit was purchased from R&D Systems, Inc. (Minneapolis, MN). Other materials and chemicals were obtained from Sigma Chemical Co. (St. Louis, MO) or Nacalai Tesque, Inc. (Kyoto, Japan). $PGF_{2\alpha}$ was dissolved in ethanol. TPA was dissolved in dimethyl sulfoxide. The maximum concentration of ethanol or dimethyl sulfoxide was 0.1%, which did not affect VEGF assay or Western blot analysis.

Cell culture

MC3T3-E1 cells are a clonal osteoblastic cell line derived from newborn mouse calvaria [24], and reportedly form mineralized matrix. In addition, we previously reported that MC3T3-E1 cells secrete osteocalcin [25] and express alkaline phosphatase [26] under our experimental conditions. MC3T3-E1 cells were maintained as previously described [27]. The cells were cultured in α-minimum essential medium (α-MEM) containing 10% fetal calf serum (FCS) at 37 °C in a humidified atmosphere of 5% CO_2/95% air. The cells were seeded into 35 mm (5×10^4) or 90 mm (2×10^5) diameter dishes in α-MEM containing 10% FCS. After five days, the medium was exchanged for α-MEM containing 0.3% FCS. The cells were used for experiments after 48 h.

Assay for VEGF

The cells were pretreated with various doses of minodronate or vehicle for 8 h, then stimulated by $PGF_{2\alpha}$ or TPA in 1 ml of α-MEM containing 0.3% FCS for the indicated period. In addition, mevalonate was added 8 h prior to stimulation by $PGF_{2\alpha}$ to investigate the involvement of mevalonate pathway on minodronate inhibition of VEGF synthesis by $PGF_{2\alpha}$. The conditioned medium was collected, and VEGF in the medium was measured by VEGF ELISA kit.

Analysis of p44/p42 MAP kinase, MEK1/2 or Raf-1

The cultured cells were pretreated with various doses of minodronate or vehicle for 8 h, then stimulated by $PGF_{2\alpha}$ or TPA in 4 ml of α-MEM containing 0.3% FCS for the indicated period. The cells were washed twice with phosphate-buffered saline and then lysed, homogenized and sonicated in a lysis buffer containing 62.5 mM Tris/HCl, pH 6.8, 2% sodium dodecyl sulfate

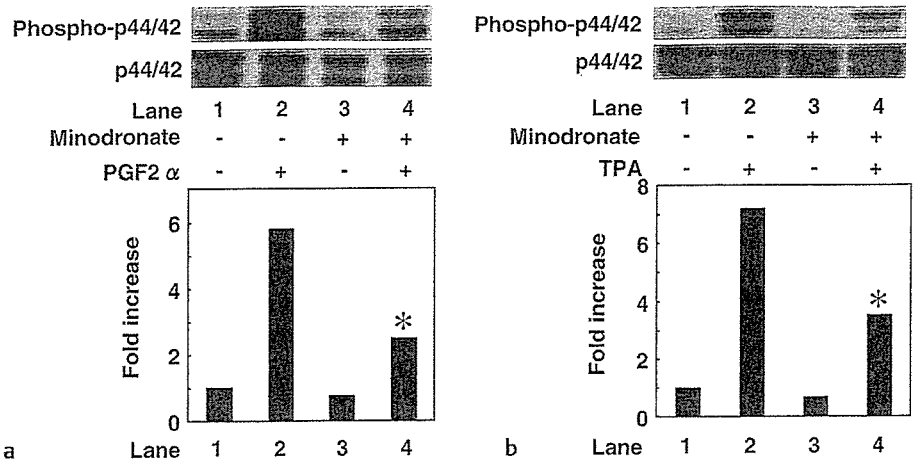


Fig. 1 Effects of minodronate on phosphorylation of p44/p42 MAP kinase induced by PGF2α or TPA in MC3T3-E1 cells. **a** Cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, then stimulated by 10 μM PGF2α or vehicle for 30 min. **b** The cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, and then stimulated by 0.1 μM TPA or vehicle for 60 min. Extracts of cells were subjected to SDS-PAGE with subsequent Western blot analysis using antibodies against phospho-specific p44/p42 MAP kinase or p44/p42 MAP kinase. The histogram shows quantitative representations of p44/p42 MAP kinase phosphorylation obtained from laser densitometric analysis. Each value represents the mean of triplicate determinations. Similar results were obtained with two additional and different cell preparations. *$p < 0.05$ compared to the value of PGF2α alone or TPA alone.

(SDS), 50 mM dithiothreitol, and 10% glycerol. SDS-PAGE was performed as described by Laemmli [28] in 10% polyacrylamide gel. Western blotting analysis was performed as described previously [29] using phosphospecific p44/p42 MAP kinase antibodies, p44/p42 MAP kinase antibodies, phosphospecific MEK1/2 antibodies, MEK1/2 antibodies, phosphospecific Raf-1 antibodies or β-actin antibodies, with peroxidase-labeled antibodies raised in goat anti-rabbit IgG used as second antibodies. Peroxidase activity on the nitrocellulose sheet was visualized on x-ray film using the ECL Western blotting detection system.

Determination of absorbance and densitometric analysis

Absorbance of ELISA samples was measured at 450 nm with a microplate spectrophotometer (Bio-Rad Laboratories, Hercules, CA). Densitometric analysis was performed using scanner and image analysis software (image J version 1.32).

Statistical analysis

Data were analyzed by ANOVA followed by Bonferroni's method for multiple comparisons between pairs, and values of $p < 0.05$ were considered significant. All data are presented as the mean ± SD from triplicate determinations. Each experiment was repeated three times with similar results.

Results

Effect of minodronate on PGF2α-induced VEGF synthesis in MC3T3-E1 cells

Recently, we have reported that $PGF_{2\alpha}$ induces VEGF synthesis in osteoblast-like MC3T3-E1 cells, and that incadronate amplifies VEGF synthesis while alendronate fails to affect synthesis [22]. Thus, we investigated the effect of minodronate on $PGF_{2\alpha}$-induced VEGF synthesis in these cells. Minodronate alone had little affect on VEGF levels, but significantly suppressed $PGF_{2\alpha}$-induced VEGF synthesis in MC3T3-E1 cells (49.1 ± 1.2 pg/ml for control; 33.1 ± 2.5pg/ml for 10μM minodronate alone, 1142.7 ± 186.5 pg/ml for 10μM $PGF_{2\alpha}$ alone; and 67.0 ± 5.5* pg/ml for 10 μM $PGF_{2\alpha}$ with 10 μM minodronate pretreatment, as measured during stimulation for 48 h; *$p < 0.05$, compared with the value of $PGF_{2\alpha}$ alone). The inhibitory effect of minodronate was dose-dependent between 3 and 100 μM (data not shown). Minodronate almost completely inhibited the $PGF_{2\alpha}$ effect at a dose of 10 μM. We confirmed that the cell number changed little by treatment [$(8.1 \pm 0.2) \times 10^5$ cells before incubation; $(7.9 \pm 0.4) \times 10^5$ cells after 48 h incubation with 100 μM minodronate; $(8.0 \pm 0.3) \times 10^5$ cells after 48 h incubation with vehicle].

Effects of minodronate on PGF2α-induced or TPA-induced phosphorylation of p44/p42 MAP kinase in MC3T3-E1 cells

In a previous study, we have demonstrated that $PGF_{2\alpha}$-induced VEGF synthesis is activated via p44/p42 MAP kinase in a PKC-dependent manner in MC3T3-E1 cells [22]. Therefore, we then investigated the detailed mechanism of minodronate underlying the inhibition of VEGF synthesis. Minodronate, which alone had little effect on phosphorylation of p44/p42 MAP kinase, markedly suppressed $PGF_{2\alpha}$-induced p44/p42 MAP kinase phosphorylation (Fig. **1 a**). According to densitometric analysis, minodronate (10 μM) caused a reduction of approximately 65% in the $PGF_{2\alpha}$ effect (*$p < 0.05$, compared with the value of $PGF_{2\alpha}$ alone).

To elucidate whether or not the effect of minodronate is exerted at a point downstream of PKC, we examined the effect of minodronate on phosphorylation of p44/p42 MAP kinase induced by TPA, a direct activator of PKC [30]. Previously, we found that p44/p42 MAP kinase was markedly phosphorylated by TPA by itself [31]. Minodronate significantly reduced p44/p42 MAP kinase phosphorylation stimulated by TPA (Fig. **1 b**). According to densitometric analysis, minodronate (10 μM) caused approximately 60% reduction in TPA effect (*$p < 0.05$, compared with the value of TPA alone).

Effect of minodronate on TPA-induced VEGF synthesis in MC3T3-E1 cells

Previously, we reported that TPA alone stimulated VEGF synthesis in osteoblast-like MC3T3-E1 cells [22]. Therefore, we investigated the effect of minodronate on TPA-induced VEGF synthesis. Minodronate significantly reduced TPA-induced syn-

Table 1 Effect of mevalonate minodronate on the TPA-induced VEGF synthesis in MC3T3-E1 cells

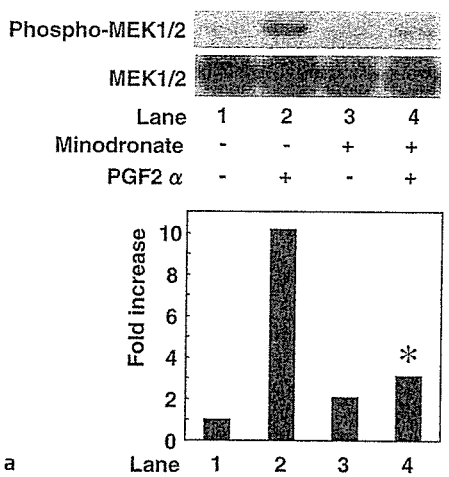
Minodronate	*TPA*	*VEGF (pg/ml)*
–	–	16±3
–	+	280±25
+	–	13±2
+	+	59±10*

Cultured cells were pretreated with 30 μM minodronate or vehicle for 8 h, then stimulated by 0.1 μM TPA or vehicle for 48 h. Cell viability after treatment was more than 90% of control cells. Each value represents the mean ± SD of triplicate determinations. Similar results were obtained with two additional and different cell preparations. *$p < 0.05$ compared to the value of TPA alone.

thesis of VEGF (Table 1). Minodronate (30 μM) caused a reduction of approximately 80% in TPA effect (*$p < 0.05$, compared with the value of TPA alone).

Effects of minodronate on phosphorylation of MEK1/2 induced by PGF2α or TPA in MC3T3-E1 cells

Activation of p44/p42 MAP kinase is known to be regulated by MEK1/2 as a MAP kinase kinase, which is regulated by an upstream kinase known as Raf-1 [32]. We have previously found that $PGF_{2\alpha}$ or TPA stimulates phosphorylation of both MEK1/2 and Raf-1 in osteoblast-like MC3T3-E1 cells [22]. Thus, we next examined the effect of minodronate on phosphorylation of MEK1/2 induced by $PGF_{2\alpha}$. Minodronate, which alone did not affect phosphorylation of MEK1/2, significantly suppressed $PGF_{2\alpha}$ induced MEK1/2 phosphorylation (Fig. **2a**, *$p < 0.05$, compared with the value of $PGF_{2\alpha}$ alone). In addition, TPA-induced phos-



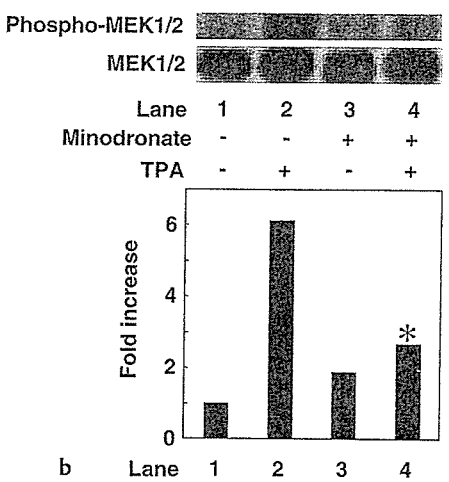
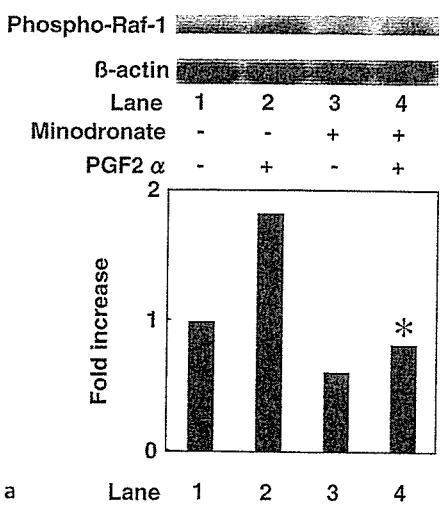


Fig. 2 Effects of minodronate on phosphorylation of MEK1/2 induced by PGF2α or TPA in MC3T3-E1 cells. (A) Cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, then stimulated by 10 μM $PGF_{2\alpha}$ or vehicle for 30 min. (B) The cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, then stimulated by 0.1 μM TPA or vehicle for 60 min. Extracts of cells were subjected to SDS-PAGE with subsequent Western blot analysis using antibodies against phosphospecific MEK1/2 or MEK1/2. The histogram shows quantitative representations of MEK1/2 phosphorylation obtained from laser densitometric analysis. Each value represents the mean of triplicate determinations. Similar results were obtained with two additional and different cell preparations. *$p < 0.05$, compared to the value of $PGF_{2\alpha}$ alone or TPA alone.



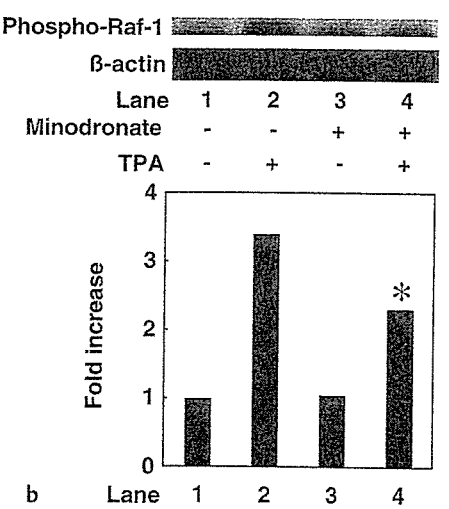


Fig. 3 Effects of minodronate on phosphorylation of Raf-1 induced by PGF2α or TPA in MC3T3-E1 cells. (**a**) The cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, then stimulated by 10 μM $PGF_{2\alpha}$ or vehicle for 15 min. (**b**) The cultured cells were pretreated with 10 μM minodronate or vehicle for 8 h, then stimulated by 0.1 μM TPA or vehicle for 60 min. Extracts of cells were subjected to SDS-PAGE with subsequent Western blot analysis using antibodies against phosphospecific Raf-1 or β-actin. The histogram shows quantitative representations of MEK1/2 phosphorylation obtained from laser densitometric analysis. Each value represents the mean of triplicate determinations. Similar results were obtained with two additional and different cell preparations. *$p < 0.05$ compared to the value of $PGF_{2\alpha}$ alone or TPA alone.

Table 2 Effect of mevalonate on minodronate inhibition of PGF2α-induced VEGF synthesis in osteoblast-like MC3T3-E1 cells

Minodronate	*Mevalonate*	*PGF2α*	*VEGF (pg/ml)*
–	–	–	33.0 ± 4.4
–	–	+	1095.0 ± 78.0
–	+	–	26.0 ± 4.5
–	+	+	1188.0 ± 282.1
+	–	–	16.0 ± 3.4
+	–	+	94.7 ± 4.2*
+	+	–	17.0 ± 3.5
+	+	+	81.3 ± 4.5*

Cultured cells were pretreated with 10 μM minodronate, 10 μM mevalonate or vehicle for 8 h, then stimulated by 10 μM $PGF_{2\alpha}$ or vehicle for 48 h. The cell viability after the treatments was more than 90% of control cells. Each value represents the mean ± SD of triplicate determinations. Similar results were obtained with two additional and different cell preparations. *$p < 0.05$, compared to the value of $PGF_{2\alpha}$ alone.

phorylation of MEK1/2 was markedly attenuated (Fig. **2b**, *$p < 0.05$, compared with the value of TPA alone).

Effects of minodronate on phosphorylation of Raf-1 induced by PGF2α or TPA in MC3T3-E1 cells

Previously, we reported that $PGF_{2\alpha}$ or TPA stimulated phosphorylation of Raf-1 in osteoblast-like MC3T3-E1 cells [22]. To clarify whether the effect of minodronate is exerted at a point upstream of Raf-1 or not, we examined the effect of minodronate on phosphorylation of Raf-1 induced by $PGF_{2\alpha}$ or TPA. Minodronate by itself did not affect Raf-1 phosphorylation, but significantly reduced phosphorylation of Raf-1 induced by $PGF_{2\alpha}$ (Fig. **3a**) or TPA (Fig. **3b**) (*$p < 0.05$, compared with the value of $PGF_{2\alpha}$ alone or TPA alone). According to densitometric analysis, minodronate (10 μM) caused a reduction of approximately 60% in the effect of $PGF_{2\alpha}$.

Effects of mevalonate on minodronate inhibition of PGF2α-induced VEGF synthesis in MC3T3-E1 cells

To clarify whether the mevalonate pathway is involved in minodronate inhibition of VEGF synthesis by $PGF_{2\alpha}$, we investigated the effect of mevalonate on the inhibition of VEGF synthesis by $PGF_{2\alpha}$ in MC3T3-E1 cells. Mevalonate, which alone had no effect on VEGF levels, did not affect either VEGF synthesis induced by $PGF_{2\alpha}$ or minodronate inhibition of $PGF_{2\alpha}$-induced VEGF synthesis (Table **2**).

Discussion

In contrast to the inhibitory effect of minodronate presented here, we have recently reported that incadronate, a nitrogen-containing bisphosphonate, but not alendronate enhances VEGF synthesis induced by $PGF_{2\alpha}$ in osteoblast-like MC3T3-E1 cells [22]. In contrast, we have recently reported that non-amino-bisphosphonate tiludronate, but not etidronate, inhibits $PGF_{2\alpha}$-induced VEGF release [23]. Thus, these findings suggest that the effects of bisphosphonates on $PGF_{2\alpha}$-induced VEGF synthesis in osteoblasts are compound-specific and vary among bisphosphonates. Pamidronate and zoledronate reportedly induce avascular

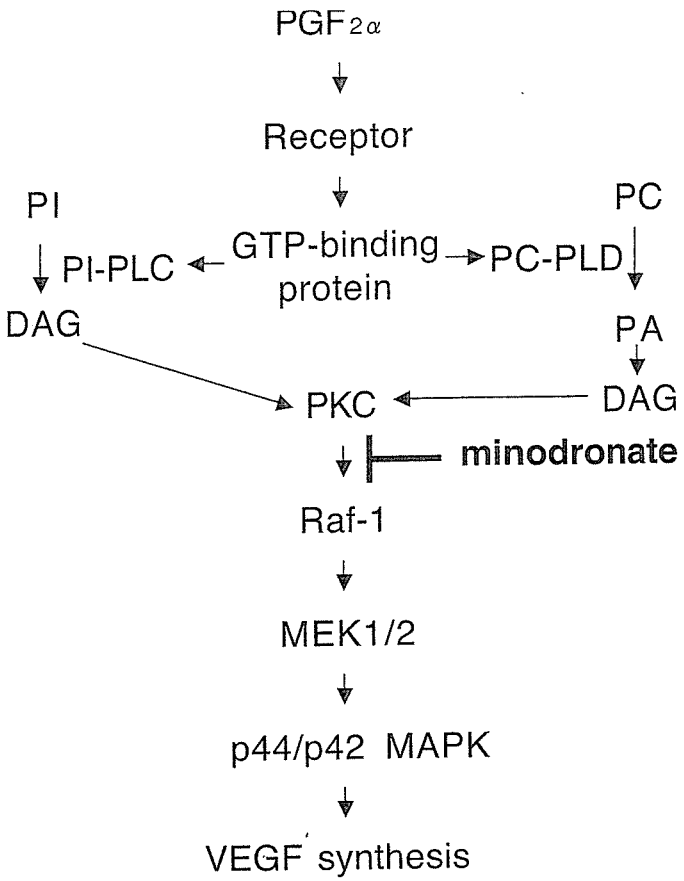


Fig. 4 Potential mechanisms in minodronate suppression of PGF2α-induced VEGF synthesis in MC3T3-E1 cells. GTP-binding protein, heterotrimeric GTP-binding protein; PI-PLC, phosphoinositide-hydrolyzing phospholipase C; PC-PLD, phosphatidylcholine-hydrolyzing phospholipase D,; PA, phosphatidic acid; DAG, diacylglycerol; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor.

necrosis of the jaw in a clinical setting [33,34], but no other bisphosphonates – including tiludronate and etidronate – are associated with avascular necrosis [33]. Taken together, the specific effects of each agent may be involved in clinical applications, supporting our present findings showing the agent-specific effects of bisphosphonates.

We previously reported that $PGF_{2\alpha}$ activated both PI-phospholipase C and PC-phospholipase D via heterotrimeric GTP-binding protein in osteoblast-like MC3T3-E1 cells [18,19], and also that $PGF_{2\alpha}$ activated p44/p42 MAP kinase in a PKC-dependent manner in these cells [35]. PI hydrolysis by phospholipase C and PC hydrolysis by phospholipase D are recognized as two major PKC-activating pathways [20,21]. In addition, we reported that $PGF_{2\alpha}$-induced VEGF synthesis through PKC-dependent, and probably PKCβI-dependent activation of p44/p42 MAP kinase in MC3T3-E1 cells [22]. Thus, we investigated the mechanism of minodronate underlying the inhibition of $PGF_{2\alpha}$-induced VEGF synthesis.

It is generally recognized that p44/p42 MAP kinase is activated through phosphorylation of threonine and tyrosine residues by dual-specificity MAP kinase kinase, known as MEK1/2 [32]. MEK1/2 is known to be activated by its own phosphorylation in-

duced by MAP kinase kinase kinase, Raf-1 [32]. We have demonstrated that minodronate also suppresses $PGF_{2\alpha}$ or TPA-induced phosphorylation of MEK1/2 and Raf-1. Taking our results as a whole, it is most likely that minodronate exerts its suppressive effect at the point between PKC and Raf-1 in $PGF_{2\alpha}$-stimulated VEGF synthesis in osteoblast-like MC3T3-E1 cells (Fig. 4).

In the previous study, we reported that incadronate enhanced [22], while tiludronate suppressed [23] $PGF_{2\alpha}$-induced VEGF synthesis in MC3T3-E1 cells. Interestingly, the amplifying and suppressive effects of incadronate and tiludronate are exerted at a point between PKC and Raf-1 [22,23], where minodronate also showed suppressive effect in the present study. These findings suggest the different molecular mechanisms among the actions of bisphosphonates on osteoblasts, most likely their structural differences. There are considerable structural differences among these agents at the R2 side chain. Minodronate possesses 1-hydroxy-2-imidazo-(1, 2-a) pyridin-3-ylethylidene structure, and incadronate possess cycloheptylaminomethylene and 1-hydroxyethylidene structures [4], and tiludronate possesses (4-chlorophenyl) thiolmethylene structure with a more simple non-nitrogen-containing R2 side chain. In addition, the different effects of these bisphosphonates on VEGF synthesis may be related to their relative potency on anti-bone resorptive activities in these agents. In metabolic bone diseases, bone remodeling rates vary from case to case. To clarify the unique agent-specific effect(s) among bisphosphonates, it may be possible to select bisphosphonates according to the specific effect on bone-forming cells in adequate therapy by these drugs. Our present data together with our previous studies [22,23] would provide a new insight into the differences in pharmacological effects among bisphosphonates possibly due to their structural differences at the R2 side chain. Further investigation would be required to clarify the exact mechanism of bisphosphonate action on bone cells.

Nitrogen-containing bisphosphonates including minodronate are known to affect the mevalonate pathway and inhibit farnesyl diphosphate synthase [4]. We found that mevalonate did not affect the suppressive effect of minodronate on VEGF synthesis by $PGF_{2\alpha}$ in MC3T3-E1 cells. Therefore, it seems unlikely that mevalonate pathway is involved in the suppressive effect of minodronate on VEGF synthesis by $PGF_{2\alpha}$ in osteoblast-like MC3T3-E1 cells. In the present study, the effect of minodronate was significant at considerably higher doses than in clinical use. According to pharmacokinetic studies on bisphosphonates, these agents mainly accumulate in bone tissue *in vivo*[4]. Minodronate concentrations in the region probably reach much higher levels than do serum concentrations. Therefore, it is possible that the effect of minodronate shown here might be implicated in clinical relevance.

In conclusion, our present data strongly suggest that minodronate suppresses VEGF synthesis stimulated by $PGF_{2\alpha}$ in osteoblasts, and the inhibitory effect is exerted at the point between PKC and Raf-1.

Acknowledgments

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1．大腿骨頸部骨折

大腿骨頸部骨折は重篤度と頻度からみて最大の骨粗鬆症合併症であり，それによる生命，機能，生活の質（QOL：quality of life）損失には大きなものがあり，その医療と介護には莫大な費用が必要である。それらの医療経済的評価には，死亡だけでなく，生存期間のQOLが重要で，治療法の正しい評価にもQOLで補正された生存年あたりの費用が必要である[1]。その参考となるべく，ここでは大腿骨頸部骨折の予後とQOLについて記述する。

大腿骨頸部骨折の合併症

1）急性期合併症

入院中合併症の発生率は，米国における大腿骨頸部骨折患者510名の研究によれば43%で，頻度順に電解質バランス不良(11%)，尿路感染（10%），呼吸器系障害（10%），譫妄（9%）であった[2]。わが国でもほとんど同じ率が報告されており，大腿骨頸部骨折525例において術後の合併症は44%に生じて，譫妄が9.3%，循環器疾患4.4%，肺炎が3.2%であった[3]。日本整形外科学会による大腿骨頸部/転子部骨折診療ガイドラインによれば，日本の多くの報告から，わが国の術後合併症は，肺炎が最も多く，次いで心不全としている[4]。性別では，別の983例の調査で，男性は，術後合併症発生率が21.4%と女性の13.8%より高く，術後合併症の危険因子となっていた[5]。合併症による入院中死亡率は，日本整形外科学会の骨粗鬆症委員会による1999年より2001年発生分の定点観測によると，3年間で集められた12,250例のうち，409名が入院中死亡し3.3%であった[6]。入院中死亡の原因はやはり肺炎が30～44%で最も多い[4]。ちなみに譫妄は，12研究1,823例によるシステマティックレビューでは，頻度は35%と高く，その危険因子は老齢と認知症だけであった[7]。

2）慢性期合併症

骨折そのものに由来する合併症としては偽関節があり，その発生率は，大腿骨頸部内側骨折の非転位型で0～15%，転位型では4～40%とされ，大腿骨転子部骨折では0.8～2.9%とされる[4]。また，大腿骨頸部内側骨折後の骨頭壊死で骨頭陥没にいたる率は，非転位型で0～8%，転位型で26～41%とされる[4]。さらに，人工骨頭施行後には22.4%に異所性骨化が発生しており，骨化が重症の例では歩行能力が低下するとされる[8]。

全身合併症は，高齢で脆弱な患者が多いため様々な疾患が起こりうるが，死因となる合併症としては，肺炎[9~12]，心不全[9~11]，脳血管障害[9,10]，悪性腫瘍[12]などが主なものである。しかし，大谷のロジスティック解析では，これらの合併症の退院後死亡への関連性は消失し，退院時歩行不能だけがオッズ比5.4の危険因子として残ったとされ[13]，機能予後と生命予後が密接に関連していることがうかがえる。

大腿骨頸部骨折の予後

1）生命予後

骨粗鬆症による骨折の中で，大腿骨頸部骨折は前述したような合併症発生も多く，生命予後に最も影響する。デンマークのJensenらは1979年に大腿骨頸部骨折患者1,592例を調査して，骨折後死亡率が3カ月で17%，6カ月で22%，1年で27%，5年で56%と，骨折後の生存曲線が骨折後1.6年までは期待生存曲線より急峻に低下し，その後は期待生存曲線と平行に推移するとしている[14]。どの年代でも大腿骨頸部骨折直後は死亡率が一般住民より上昇し，それ以後6カ月以降まで下降するが，その後も一般住民より高率にとどまる[15]というパターンは時代と国を越えて共通のものと考えられる。ただし，その内容は社会情勢に左右されて異なっており，死亡率は北欧，日本では時代とともに改善しているが，英国ではあまり変わらず[16]，2005年に英国のRocheらが大腿骨頸部骨折2,090例を前向き調査した報告をみても，骨折後死亡率は術後30日で9.6%，1年で33%と相変わらず高いレベルにとどまっている[17]。

わが国では，七田らの1988年の研究が最初で，1,048例中867例を追跡し，死亡率は6カ月で8%，1年で14%，2年で35%と報告

している[10]。他の1年死亡率に関する報告としては，1990年の松林らの13%[11]，1991年の水野らの16%[18]，1995年の関らの18%[19]，1998年の大田らの14%[20]などがある。前述した日本整形外科学会による1999年から3年間発生分の定点観測では，12,250例が縦断研究され，解析可能だった11,876例は，平均79.4歳で1年後に1,120例が死亡しており，1年後死亡率は9.1%であった。この率は受傷年別にみると，1999年9.7%，2000年9.4%，2001年8.3%と年々低下していた[6]。3年間で在院日数は1999年59日，2000年49日，2001年48日と年々低下している中で死亡率が改善しており，周術期管理や早期リハビリテーションおよび退院後も継続される医療・介護など，適切なケアの向上がこのような成果をもたらしたものと考えられる。

このように改善しつつあるとはいえ，大腿骨頸部骨折後の死亡率増加は明らかで，それには多くの因子が関連すると考えられるが，まず年齢の高いことがあげられる。前述の日本整形外科学会の定点観測をみても，1年後死亡率は年代別に，50歳代で2.1%，60歳代で5.1%，70歳代で7.6%，80歳代で14.1%，90歳代で21.3%，100歳代で36.1%と，高齢なほど高かった[6]。次に，受傷前すでに健康不良であることがあげられる。前述の英国の研究の結果，術後30日の死亡率上昇に関連する術前要因は，3つ以上の併存疾患，呼吸器疾患，悪性腫瘍疾患の存在だったが，最も強い予測因子は3つ以上の術前併存疾患であった[17]。しかし，2004年のフランスの研究[21]および2005年のスウェーデンの研究[22]では，大腿骨頸部骨折の骨折後死亡リスクは，年齢と健康状態を補正しても骨折のない人より2倍以上高く，大腿骨頸部骨折による死亡率はこれらの因子に関連なく増加していた。さらに，男性であることは，急性期のみならず全期間を通じて大腿骨頸部骨折後の死亡率増加の危険因子で，男性大腿骨頸部骨折患者105例を3.6年追跡した結果，生存年数減少の比率は男性のほうが高く，生存に対する大腿骨頸部骨折のインパクトは男性のほうが大きいことが示されている[23]。また，認知症の併存は生命予後を悪化させることも知られている。1年後死亡率は，認知症のない患者において，米国の研究で18%[24]，日本の研究[11]で13%だったのに対して，認知症のある患者では，それぞれ47%と

37%まで悪化しており，認知症特有の理解と意欲の欠乏が機能回復を妨げ，生命予後にも影響を及ぼしているものと思われる。加えて，歩行能力も骨折後の死亡率悪化に関連しており，米国においては骨折後歩行能力が回復した例の1年後死亡率は8％で，歩行能力が回復しなかった例の40%より低いと報告されている[24]。わが国でも退院時屋外歩行が可能となった例の5年後死亡率は33%で，不能であった例の74%より低かったとされている[12]。

2）機能予後

大腿骨頸部骨折後には，歩行能力をはじめとした重要な機能の低下が残存して自立が損なわれる可能性が高いことはよく知られている。当然ではあるが，受傷後早期では機能回復不良は甚だしく，退院後4カ月では，たった18%の患者しか骨折前の機能に戻っていなかったという報告もある[25]。その後の骨折後6～12カ月でも92例の在宅の大腿骨頸部骨折患者は，年齢，性を補正しても日常生活動作（ADL：activities of daily living）のすべてがコントロールより劣っており[26]，経時的に回復は進むものの，最終的に受傷前の機能を再獲得する率は高くない。欧米の研究では，受傷前に歩行できた大腿骨頸部骨折患者の実に半数が骨折後自立した歩行能力を失い，受傷前に自立して生活できた患者のやはり半数が骨折後，日常生活上の介護・支援を長く受けるようになり，最終的に介護度が悪化して施設入所のリスクが1/3以上で高まるとされる[27]。

わが国での大腿骨頸部骨折後の機能予後については，七田らの研究が最初で，1973年から1984年までに東京都老人医療センターを退院した大腿骨頸部骨折1,048例のうち，867例を4.1年追跡したところ，54%が生存しており，寝たきり24%，寝たり起きたり15.5%，起きているが歩けない14%としている[10]。このデータと同時に示された80歳代の非骨折者における自立度の分布，寝たきり5.4%，寝たり起きたり4.3%という分布から，太田は，大腿骨頸部骨折患者と非骨折者の差が骨折による変化と仮定して，大腿骨頸部骨折による寝たきりの発症は18.8%，寝たり起きたり11.2%，起きているが歩けない12%となり，これらを合計すると42%にもなるとしている[28]。

ただし，わが国では，周術期管理や早期リハビリテーションおよ

び退院後も継続される医療・介護における適切なケアの向上が機能予後をも改善しているようで，1998年には，日本人の大腿骨頸部骨折1,217例のうち，受傷後1年で受傷前歩行能力に回復したのは67%という良好な報告もみられ[29]，さらに，前述した日本整形外科学会の定点観測研究によれば，受傷後1年で受傷前のADLに回復したのは，3年間全体で65%であったが，経時的推移をみると，1999年で61%，2000年で64%，2001年68%と年々増加していた。逆にADLが悪化していたのは，1999年で39%，2000年で35%，2001年31%と年々減少していた[6]。このように，大腿骨頸部骨折後の生命予後と同様に機能予後も着実に改善しているようである。

大腿骨頸部骨折のQOL

大腿骨頸部骨折による生命予後や機能予後の悪化については，前述したとおりであるが，生存する患者にとって最も重要なものは，骨折後にもたらされる心理的障害も含むQOLの低下である。したがって，それを客観的に捉えて定量化，標準化することは，実態を明らかにし，治療の効果を明確にするうえで大変重要であると考えられる。Tostesonらは，健康に関連したQOLについて，50歳以上の骨粗鬆症性骨折のない女性と脊椎や大腿骨頸部の骨折のある女性を健康の自己評価とSF-36（MOS Short Form 36）を用いて比較した。その結果，質調整生存年（QALY：quality-adjusted life-year）に換算するための選考ウェイトは，脊椎骨折を1つ以上有すると0.82，大腿骨頸部骨折があると0.63と，骨折のない場合の0.91より有意に低く，年齢，ホルモン補充療法（HRT：hormone replacement therapy）で補正後も有意な差が認められたとしている[30]。

大腿骨頸部骨折のQOLについて，骨折後6～12カ月での横断研究では，対照92例と比較して在宅大腿骨頸部骨折患者92例は，年齢，性を補正後もSF-36の8ドメインすべてが低く，骨折後のバランスと運動の障害は，機能的および社会的自立の損失とともにQOLを低下させ，多くの骨折患者が受傷前のライフスタイルに戻れないことを示唆した[31]。

縦断研究では，萩野がEQ-5D（EuroQOL）を使用して大腿骨頸部骨折患者を追跡して，EQ-5Dの効用値が，骨折手術後2週では骨折

前より約50%低下し，3カ月では機能回復に伴って骨折前の20%低下にまで改善していることを示した[32]。同じEQ-5Dによる追跡をTidermarkらが大腿骨頸部骨折67例に対して骨折後17カ月まで行い，EQ-5D効用値は，骨折前の記憶による0.78から4カ月で0.59，17カ月で0.51まで低下しているが，大腿骨頸部骨折患者のQOLはやはり受傷前レベルまでには回復しないことを報告している。このQOL低下には，骨折治癒不良，疼痛継続，運動機能不良など様々な要因が関与していた。骨折治癒過程の合併症の有無，疼

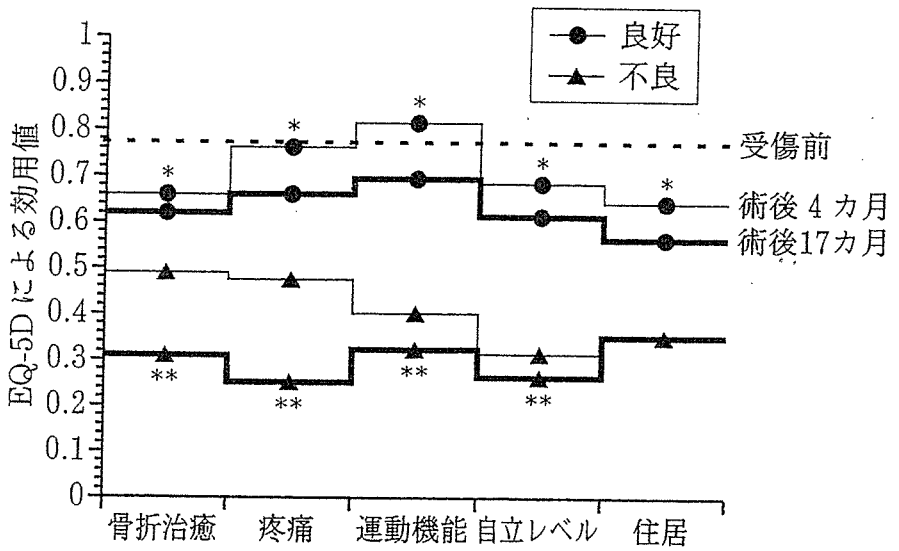

図1　EQ-5Dによる大腿骨頸部骨折患者におけるQOLの要因別推移

骨折治癒，疼痛，運動機能，自立レベル，住居（介護施設かそれ以外）が良好な人は●，不良な人は▲で示し，破線は受傷前，細い線は術後4カ月，太い線は術後17カ月を表す。各要因の良否で観察すると，大腿骨頸部骨折患者のEQ-5D効用値は，疼痛と運動機能の回復が良好な人は，術後4カ月（細い線）で受傷前まで回復するが，術後17カ月（太い線）には，各要因の良好な人でも受傷前より低下している。各要因が不良な人は良好な人と比較してどの時期でも明らかなQOL低下がみられる。

*：術後4カ月で各要因の良否で有意差があったもの，**：術後17カ月で各要因の良否で有意差があったもの

EQ-5D：EuroQOL，QOL：quality of life（生活の質）

（文献33より引用改変）

痛が視覚アナログ尺度（VAS：visual analogue scale）30 mm 以下と 30 mm 以上，運動機能が 1 本杖歩行以上と歩行器歩行以下，自立レベルの高低，住居の独居と介護施設で比較すると，EQ-5D 効用値は，術後 4 カ月ではすべての要因で不良な人は良好な人より有意に低く，術後 17 カ月後でも，住居以外の要因では不良な人が有意に低かった（図 1）[33]。早期の内固定材トラブル，骨癒合不全，無腐性骨壊死などの骨折治癒過程の合併症の可及的防止の重要性を改めて認識させられる。

アジアにおける大腿骨頸部骨折の QOL 縦断調査として，台湾の大腿骨頸部骨折 110 例を SF-36 にて 1 年追跡した研究がある。それによると，大腿骨頸部骨折患者は，退院後 1 カ月では在宅者の 77.5 と比較して 63.8 と低値であった。ドメイン別にみると，1 カ月ではほとんどのドメインでスコアが低く，特に身体機能と日常役割機能では身体的問題によって最低であった。3 カ月までに全体的健康感以外は，各ドメインは改善した。身体機能は以後 6 カ月まで有意に改善が続き，日常役割機能は身体的問題のため 3 カ月から 6 カ月まで平行線となるが，それ以後 1 年まで再び有意に改善した。残りのドメインは 3 カ月から 1 年までほぼ変わらないままであった（図 2）[34]。

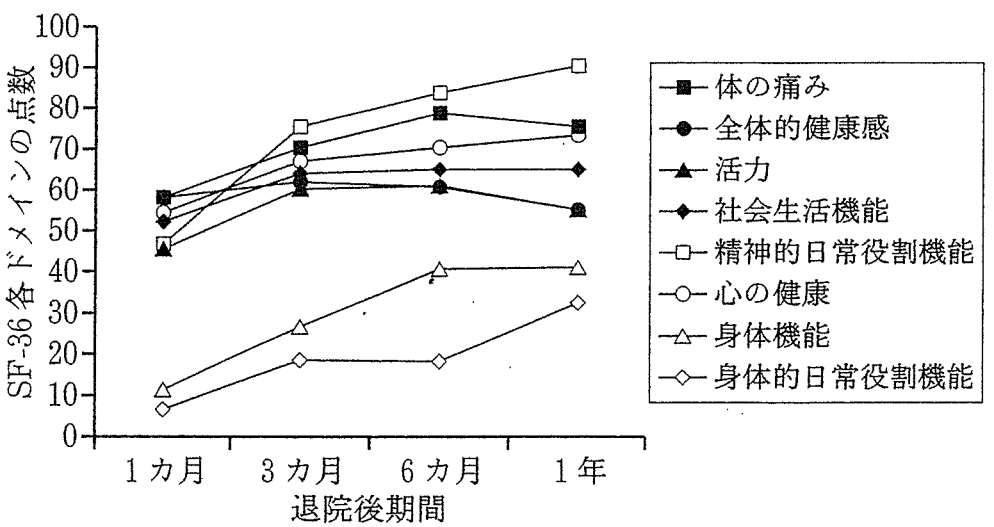

図 2　SF-36 による大腿骨頸部骨折の QOL 変化

台湾の大腿骨頸部骨折 110 例の SF-36 の各ドメインの縦断的変化を示している。

SF-36：MOS Short Form 36

（文献 34 より引用改変）

ちなみに，大腿骨頸部骨折のQOL評価の手段としてSF-36とEQ-5Dが比較され，大腿骨頸部内側骨折患者に関しては，110例での検討でSF-36とEQ-5Dの両方とも測定法として適していたとされている[35]。

大腿骨頸部骨折のQOL研究の問題点としては，認知症合併などのためにQOL評価ができない患者が多数存在することである。Boonenらの検討でも，SF-36が完全に施行できた人は51%にとどまり，できなかった人よりかなり若く，機能の高い状況であり，バイアスの発生を指摘されている[36]。

最後に，高齢化社会の進行に伴う財源不足が確実視される現在，投じた費用に見合う効用が求められるのは必定である。大腿骨頸部骨折の場合，効用はQOLで補正された獲得生存年である。したがって，骨折後のQOL追跡が必要であるが，わが国ではまだ大腿骨頸部骨折後のQOL研究は十分とはいえず，これからの進展が望まれる。

（原田　敦）

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