Comparison in bone turnover markers during early healing of femoral neck fracture and trochanteric fracture in elderly patients

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Abstract

Healing of fractures is different for each bone and bone turnover markers may reflect the fracture healing process. The purpose of this study was to determine the characteristic changes in bone turnover markers during the fracture healing process. The subjects were consecutive patients with femoral neck or trochanteric fracture who underwent surgery and achieved bone union. There were a total of 39 patients, including 33 women and 6 men. There were 18 patients (16 women and 2 men) with femoral neck fracture and 21 patients (17 women and 4 men) with trochanteric fracture. Serum bone-specific alkaline phosphatase (BAP) was measured as a bone formation marker. Urine and serum levels of N-terminal telopeptide of type I collagen (NTX), as well as urine levels of C-terminal telopeptide of type I collagen (CTX) and deoxypyridinoline (DPD), were measured as markers of bone resorption. All bone turnover markers showed similar changes in patients with either type of fracture, but significantly higher levels of both bone formation and resorption markers were observed in trochanteric fracture patients than in neck fracture patients. BAP showed similar levels at one week after surgery and then increased. Bone resorption markers were increased after surgery in patients with either fracture. The markers reached their peak values at three weeks (BAP and urinary NTX), five weeks (serum NTX and DPD), and 2-3 weeks (CTX) after surgery. The increase in bone turnover markers after hip fracture surgery and the subsequent decrease may reflect increased bone formation and remodeling during the healing process. Both fractures had a similar bone turnover marker profile, but the extent of the changes differed between femoral neck and trochanteric fractures.

Introduction

There has been considerable interest in the assessment of bone turnover using biochemical markers, and measurement of various bone turnover markers has recently become easier for clinical use. Serum bone-specific alkaline phosphatase (BAP) has been used for the evaluation of bone formation, while the breakdown products of type I collagen have been reported to be specific and sensitive bone resorption markers.[1] It is now possible to use these markers to evaluate bone turnover in patients with osteoporosis and other bone diseases.[2]

Recently, we reported that bone turnover markers were significantly increased in elderly women with back pain.[3] Vogt *et al.* reported that only one-third of patients with vertebral fractures knew of their existence.[4] In patients with osteoporosis, vertebral fractures frequently cause back pain[5-7] Therefore, evaluation of bone turnover using biochemical markers in elderly women may allow us to detect the influence of unrecognized fractures.[3] Although longitudinal changes in bone turnover markers after fracture have been reported and it has been pointed out that these markers increase during fracture healing,[8-17] there have been few investigations into the changes in bone turnover markers in patients with fragility fractures. Generally, it is considered that the process of fracture healing (amount of callus formed, time until bone union, etc.) is different for each fracture site. However, only a few studies have compared the changes in bone turnover markers between different fragility fractures. Also, although the bone resorption markers available for clinical testing have increased, there have been no reports on the responses of various bone resorption markers during the healing of fragility fractures.

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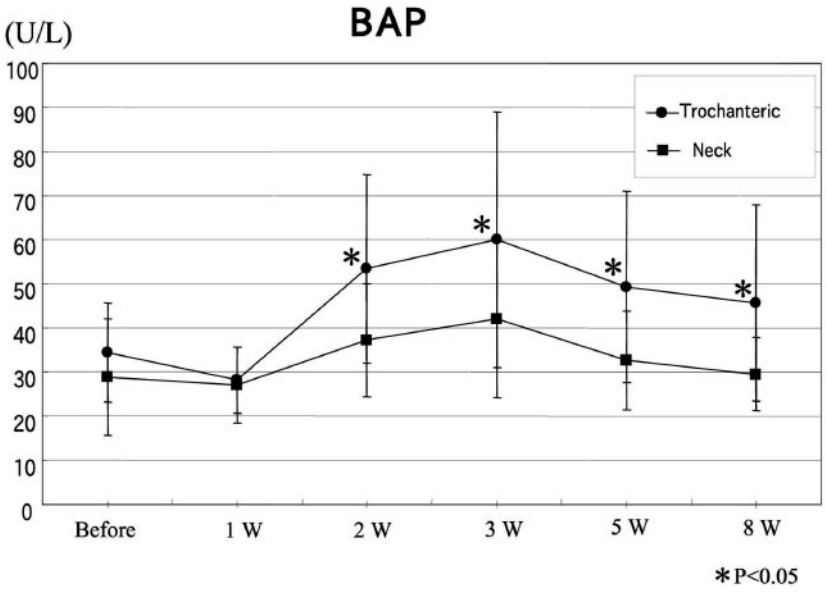

Figure 1. Time course of the serum levels of bone-specific alkaline phosphatase (BAP) in femoral neck fracture patients and trochanteric fracture patients.

Hip fractures are the most common type of fragility fracture and can cause many serious or even fatal complications in elderly patients.[18,19] Hip fractures can be divided into trochanteric and femoral neck fractures. These two types of fracture occur in adjacent parts of the proximal femur, but have quite different clinical features. It is well known that non-union is common in patients with femoral neck fractures, while it is rare in those with trochanteric fractures. We considered that these two types of hip fracture might be a useful model for assessing differences in the responses of bone turnover markers after fragility fracture. Recently, some authors have reported on the changes in bone turnover markers after femoral neck and trochanteric fractures.[9,12,13] However, there have been no reports comparing changes in bone-specific turnover markers during the healing of femoral neck and trochanteric fractures.

At Suwa Red Cross Hospital, multiple pins are used to stabilize femoral neck fractures in most patients, even when the fracture is displaced. In the present prospective study, various bone turnover markers were measured after surgery for femoral neck and trochanteric fractures, with the purpose of determining whether there were characteristic short-term changes in these markers during the healing of proximal femoral fractures.

Design and Methods

The patients in this prospective study were consecutive patients with femoral neck or trochanteric fracture who underwent surgical intervention and achieved bone union at Suwa Red Cross Hospital between January and December 2003. We performed universal hip replacement (UHR) in patients with femoral neck fractures who were in a poor physical and/or mental state. We also performed UHR in patients with subcapital fractures and excluded them from this study. Patients who were bedridden both before and after surgery due to physical and/or mental problems were also excluded.

A total of 39 patients (33 women and 6 men) were followed up after surgery and achieved bone union. They formed the participants in this study. Their age range was 56-96 years, with an average age of 78.3 years. There were 18 patients (16 women and 2 men) with femoral neck fractures and 21 patients (17 women and 4 men) with trochanteric fractures. The average age of the former group was 75.8 years and that of the latter group was 80.8 years (Table 1). All of the patients with femoral neck fractures were treated using multiple pins, while the patients with trochanteric fractures were treated using compression hip screws (CHS).

Patients with both types of fracture were permitted movement in a wheelchair as soon as possible after surgery. Patients with trochanteric fracture were usually allowed to start weight bearing from two weeks after surgery, while patients with femoral neck fractures usually commenced weight bearing from four weeks and were encouraged to gradually increase this. Bisphosphonate therapy was not initiated until eight weeks after surgery. At six months after surgery, all patients were assessed for clinical and radiological evidence of fracture healing. When radiological evidence of bridging callus, sclerosis, and/or remodeling at the fracture site was confirmed by two independent orthopedic surgeons and the patient could walk without pain we assumed that bone union was complete.

Serum BAP was measured as a bone formation marker. Urine and serum levels of N-terminal telopeptide of type I collagen (NTX), urine levels of C-terminal telopeptide of type I collagen (CTX), and urine levels of deoxypyridinoline (DPD) were measured as markers of bone resorption. The levels of NTX (Osteomark, Osteox International, Seattle, WA), DPD (Metrar DPD EIA Kit, Quidel Corporation, San Diego, CA, USA), and CTX (Frelisa, CrossLaps, Nordic Bioscience Diagnostics, A/S, Herlev, Denmark) were measured using the enzyme-linked immunosorbent assay (ELISA). At the first examination, intact parathyroid hormone (i-

Table 1. Profile of the two fracture groups.

	N. of patients	Male	Female	Age (range)	Intact PTH (pg/mL)	25(OH)VitD3 (ng/mL)
Femoral Neck	18	2	16	75.6±8.5 (56-94)	40.4±24.2	21.1±7.0
Trochanteric	21	4	17	80.8±7.7 (60-96)	41.5±15.6	19.8±7.5
p value				0.0589	0.882	0.605

Student's t-test.

Table 2. Changes in the bone turnover markers.

		Before	1 W	2 W	3 W	5 W	8 W
(U/L)Neck	Neck	28.8±12.3 (8)	27.0±8.3 (18)	37.2±12.4 (18) *	41.9±17.2 (18) *	35.0±10.9 (15) *	29.5±8.1 (15) *
	Troch.	34.4±10.8 (13)	28.1± 7.3 (21)	53.4± 20.9 (21)	60.0± 28.4 (21)	49.3± 21.1 (19)	45.7± 21.5 (16)
U-NTX (nmolBCE /mmol·CRE)	Neck	93.3± 34.4 (8)	112.0± 63.4 (18)	117.2± 68.6 (18) *	146.8± 78.9 (18) *	139.7± 69.7 (18)	125.1± 47.2 (14) *
	Troch.	129.4± 76.5 (13)	166.5± 111.9 (21)	173.8± 91.6 (21)	215.3± 93.5 (21)	186.5± 94.3 (21)	185.4± 69.2 (16)
S-NTX (nmolBCE/l)	Neck	21.0± 8.2 (6)	26.4± 11.3 (16)	25.7± 13.9 (16)	29.4± 14.5 (16)	30.0± 14.6 (16)	27.4± 9.7 (13) *
	Troch.	24.2± 6.6 (11)	26.6± 9.6 (19)	30.6± 9.9 (19)	38.3± 11.8 (19)	38.9± 10.5 (16)	35.7± 7.9 (14)
DPD (nmol/mmol ·CRE)	Neck	6.9± 2.6 (6)	9.4± 4.8 (16) *	10.3± 4.1 (16) *	11.4± 4.0 (16) *	12.3± 5.2 (16) *	11.4± 2.3 (13) *
	Troch.	10.8± 4.8 (12)	13.1± 5.3 (20)	15.7± 6.8 (20)	18.5± 8.3 (20)	21.7± 10.9 (17)	18.7± 6.7 (14)
CTX (μg/mmol ·CRE)	Neck	438± 126 (6)	532± 245 (16)	563± 286 (16) *	640± 317 (16) *	629± 262 (16)	561± 113 (13) *
	Troch.	630± 414 (12)	713± 372 (20)	933± 473 (20)	909± 420 (20)	807± 383 (17)	712± 202 (15)

Neck: Femoral neck fracture, Troch.: Trochanteric fracture. *$p < 0.05$. (n = Number of patients)

PTH) was measured in an immunoradiometoric assay and 25(OH) vitamin D (VitD) was measured in a competitive radioimmunoassay (except one case of trochanteric fracture).

In principle, samples of venous blood and spot urine were collected on the following six occasions: within 24 hours after injury, and one, two, three, five, and eight weeks after surgery. Because pre-operative data were limited, these data were excluded from the object of the examination, and showed as a reference data. The spot urine samples were collected from the second morning urine, avoiding the first morning urine. Samples were stored at -20°C until analysis. Immunoassays were performed by SRL Inc. (Tokyo, Japan).

All patients gave informed consent to undergo examination and medical treatment. This study was carried out prospectively and in accordance with the Helsinki Declaration, and approved by the ethics committees of Suwa Red Cross Hospital. Differences in the age and the bone turnover markers at each examination between patients with femoral neck and trochanteric fractures were assessed using Student's unpaired t-test. Statistical significance was set at a probability value of less than 0.05.

Results

Patients' background data are shown in Table 1. The values of i-PTH and VitD showed no significant differences between the two types of fracture. A correlation between i-PTH and VitD was observed, but it was not significant (p=0.053). All of the bone turnover markers were increased after surgery in patients with either type of fracture, but there were significantly higher values of both bone formation and resorption markers in the patients with trochanteric fractures than in those with femoral neck fractures (Table 2). All of the bone turnover markers showed a similar pattern of changes in both fractures, but the actual values in bone turnover markers was smaller in patients with femoral neck fracture than in those with trochanteric fracture.

BAP (Figure 1) showed similar levels in both fractures at one week after surgery and then increased to reach 41.9±17.2 in femoral neck fracture patients and 60.0±28.4 U/L in trochanteric fracture patients at three weeks after surgery. BAP levels were significantly higher in trochanteric fracture patients than in neck fracture patients from two weeks after surgery. In femoral neck fracture patients, BAP decreased to 29.5 U/L after eight weeks. In trochanteric fracture patients, however, BAP was 45.7±21.5 U/L at eight weeks and was still high compared with that in patients with femoral neck fractures.

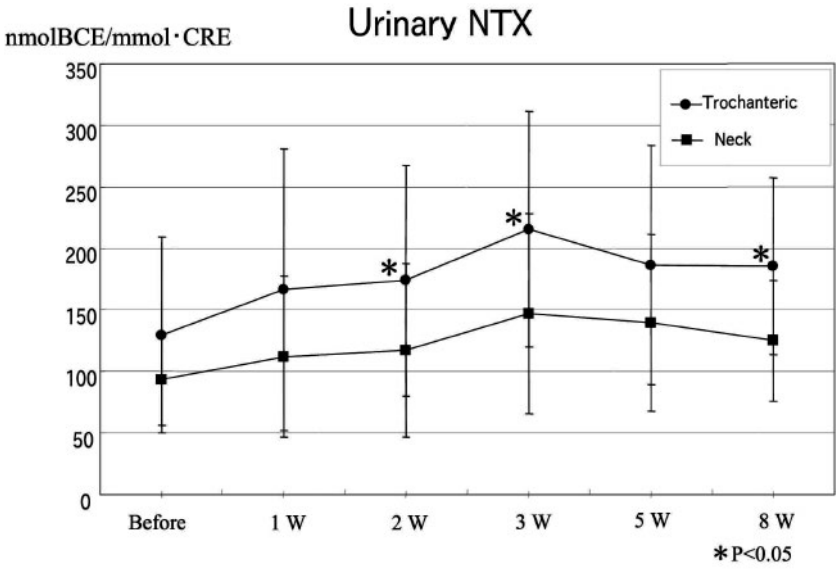

Figure 2. Time course of the urine levels of *N*-terminal telopeptide of type I collagen (NTX) in femoral neck fracture patients and trochanteric fracture patients.

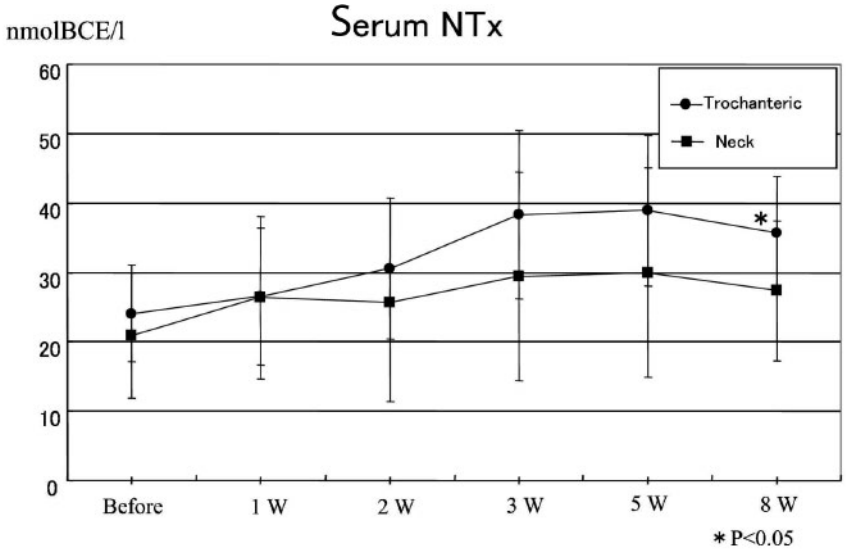

Figure 3. Time course of the serum levels of NTX in femoral neck fracture patients and trochanteric fracture patients.

Urinary NTX (Figure 2) was increased after surgery and showed a similar pattern in both fractures, but urinary NTX levels were significantly higher in trochanteric than neck fracture patients from two weeks after surgery, except at five weeks. At three weeks after surgery, urinary NTX increased to 146.8±78.9 in femoral neck fracture patients and to 215.3±93.5 from 129.4±76.5 nmolBCE/nmol·CRE in trochanteric fracture patients. Urinary NTX reached its peak at three weeks after surgery and remained high compared with the reference values until eight weeks in both types of fracture. Serum NTX (Figure 3) showed similar levels in trochanteric and femoral neck fracture patients at one week after surgery, unlike urinary NTX and the other bone resorption markers. Also unlike urinary NTX, serum NTX increased later and reached a peak at five weeks after surgery, remaining high at eight weeks. Serum NTX reached 30.6±9.9 in femoral neck fracture patients and 38.9±10.5 nmolBCE/l in trochanteric fracture patients. Serum NTX was only significantly higher in trochanteric fracture patients than in femoral neck fracture at eight weeks after surgery. Urinary and serum NTX revealed different patterns of change over time.

Urinary DPD (Figure 4) increased after surgery and showed the same pattern in both

types of fracture, but DPD levels were significantly greater in trochanteric than in femoral neck fracture patients from one to eight weeks after surgery. DPD increased to reach 12.3±5.2 in femoral neck fracture patients and 21.7±10.9 nmol/mmol·CRE in trochanteric fracture patients at five weeks after surgery.

Urinary CTX (Figure 5) increased after surgery and showed the same pattern in both types of fracture, but CTX levels were significantly greater in trochanteric fracture patients than in femoral neck fracture patients from two weeks after surgery. Urinary CTX reached 933±473 at two weeks in trochanteric fracture patients and 640±317 at three weeks in femoral neck fracture patients, after which it decreased.

At six months after surgery, all of the patients achieved bone union of each fracture site. Despite an initial diagnosis of bone union, re-evaluation of one patient with femoral neck fracture led to a subsequent diagnosis of pseudarthrosis of femoral neck after 13 months post surgery, and UHR was subsequently performed. Another patient with femoral neck fracture resulted in osteonecrosis of femoral head despite having achieved bone union of the femoral neck. No patients presented surgical site infection during the observation period.

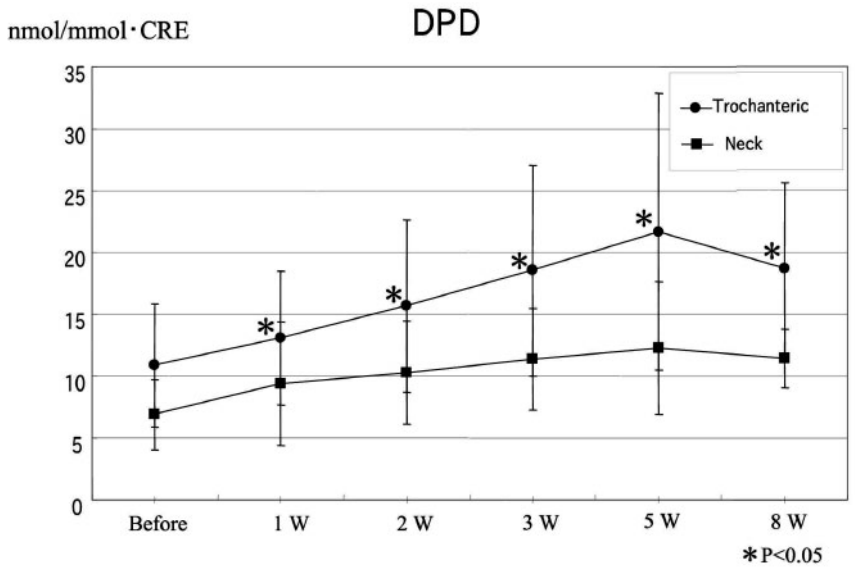

Figure 4. Time course of the urine levels of deoxypyridinoline (DPD) in femoral neck fracture patients and trochanteric fracture patients.

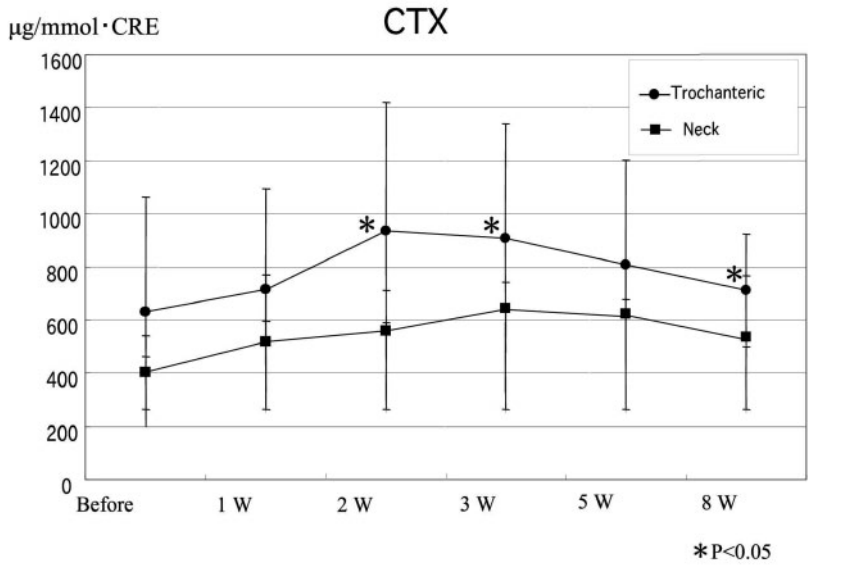

Figure 5. Time course of the urine levels of *C*-terminal telopeptide of type I collagen (CTX) in femoral neck fracture patients and trochanteric fracture patients.

Discussion

Bone turnover markers may reflect the fracture healing process. The changes in bone turnover markers during fracture healing are believed to be greater than those that occur during the physiological remodeling cycle. Many authors have reported that bone turnover markers are increased after fracture.[8-17]

Femoral neck and trochanteric fractures occur in adjacent parts of the proximal femur in elderly people, but have quite different clinical features. Therefore, we selected these two hip fractures to investigate the changes in bone turnover markers after bone fragility fracture in this prospective study. We found that each bone turnover marker had the same pattern of changes in the two different types of hip fracture. On the other hand, both bone formation and resorption markers showed significantly higher values in patients with trochanteric fracture than in those with femoral neck fracture.

Generally, it is considered that fracture might directly influence bone formation and that immobilization following fracture may induce an increase in bone resorption. Bone resorption markers are strongly related to physical activity.[20-23] Theiler *et al.* found that bone resorption markers were significantly higher in institutionalized and physically inactive patients compared with those who were ambulatory and physically active.[22] Other authors have reported that bone resorption markers are increased by bed rest,[20-23] while bone formation markers decrease with bed rest.[20] Decreased physical activity usually leads to an increase in bone resorption and the inhibition of bone formation.

The patients with trochanteric fracture in this study were older than those with femoral neck fracture, as in previous reports.[16] It was reported that in elderly women with osteoporosis, urinary NTX levels increased with aging but BAP levels did not change.[3] However, the effect of aging on bone resorption markers is slight.[3] In this study, patients with both types of fracture were permitted movement in a wheelchair as soon as possible after surgery, and patients with femoral neck fracture delayed weight bearing for longer than those with trochanteric fracture. In elderly patients, physical activity is usually decreased. And many elderly patients often have difficulty walking without weight bearing. The differences in physical activity, age, and post-operative therapy had various conflicting influences on bone resorption markers in this study.

With respect to post-operative therapy, physical activity might be slightly greater in trochanteric fracture patients than in those with femoral neck fracture. Bone resorption markers were significantly higher in the

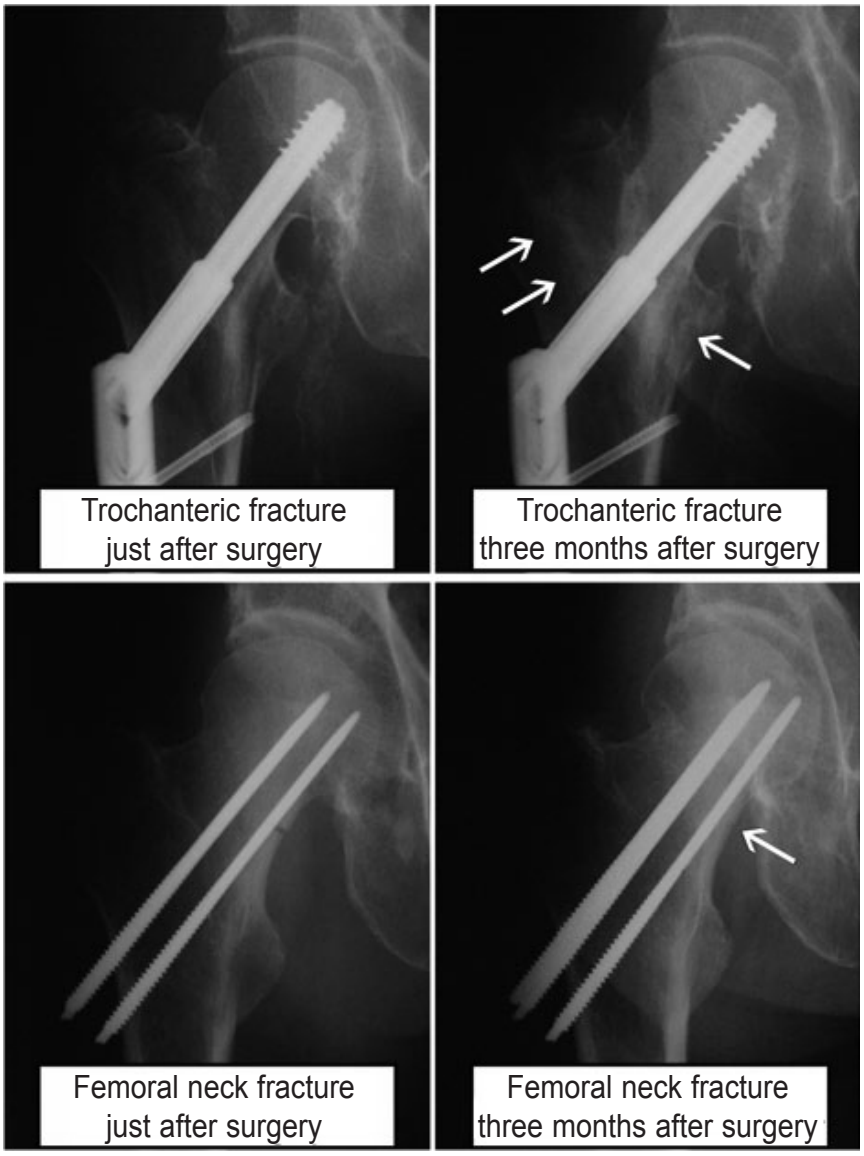

Figure 6. The difference in callus formation between trochanteric fracture and femoral neck fracture during each healing process in radiographs. In trochanteric fracture, increased radiodensity along the fracture line, which is regarded as callus formation, is observed at three months after surgery (shown by arrows). By contrast, the finding is inconspicuous in femoral neck fracture (shown by an arrow).

trochanteric fracture group than in the femoral neck fracture group despite the difference in physical activity and post-operative management. Thus, the decrease in physical activity due to post-operative therapy did not influence the changes in bone resorption markers after proximal hip fracture. Accordingly, the changes in bone resorption markers due to fracture healing might exceed those related to physical activity in elderly patients with hip fracture.

In general, it is believed that appropriate weight bearing helps bone union and it may increase bone formation. Therefore, it was hypothesized that the increase in bone formation markers might occur earlier with early weight bearing. In this study, all bone turnover markers showed the same pattern of change in both types of fracture although the time when weight bearing was initiated differed between the two patient groups. The difference in initiation of weight bearing did not affect the pattern of change in bone formation marker levels. However, bone formation marker levels in trochanteric fracture patients were significantly greater than those in femoral neck fracture patients.

In this study, multiple pinning methods were used for femoral neck fractures, and CHS was performed for trochanteric fractures. Multiple pinning surgery was performed as open surgery, like CHS. However, the surgical invasiveness of CHS is greater than that of multiple pinning methods. Evaluation of the effects of surgery based on C-reactive protein and cytokine levels was limited to a short period.[24,25] Therefore, if the degree of surgical invasiveness affects bone turnover markers, the changes in bone turnover due to different surgical procedures might be limited to a short period.

Previously, Hosking had reported that the increase in total alkaline phosphatase was similar during the healing of femoral neck and trochanteric fractures.[8] However, Nakagawa has recently reported that post-operative total alkaline phosphatase levels were significantly higher in trochanteric fracture patients than in those with femoral neck fracture during the healing process.[16] It has been reported that the fracture of small bones (such as the wrist and ankle) does not cause marked changes in bone turnover markers.[10,11] The relative extent of bone formation and remodeling during the fracture healing process would determine the changes in bone turnover markers. In patients with trochanteric fracture, radiographs show that callus formation and/or remodeling during the healing process is more extensive and dynamic than in those with femoral neck fracture (Figure 6) and these differences would be reflected in the levels of bone formation markers. Furthermore, the difference in the area of fracture might affect bone turnover markers. In the present study, bone turnover marker levels (including BAP) were significantly higher in patients with trochanteric fracture than in those with femoral neck fracture. The changes in bone turnover markers corresponded to the radiographic findings in femoral neck fracture, and the results of this study supported Nakagawa's data but not those of Hosking.

In this study, we also found that urinary and serum NTX levels had a different pattern of change. Recently, Akesson *et al.* have used a fracture model to assess changes in bone turnover markers, and they reported that serum and urinary osteocalcin (Oc) levels showed different changes after fracture[15] i.e. urinary Oc increased at 6-9 weeks but serum Oc increased at 4-7 months after surgery. From the results reported by Akesson *et al.* and the findings of our study, some bone turnover markers might show different changes in the urine and serum during fracture healing.

Based on the results of the current study, bone fragility fractures might directly affect both bone formation and resorption marker levels. The changes in bone turnover markers after fragility fracture at different sites might have a similar pattern but differ with respect to the extent of change.

In this study, pre-operative data were not obtained in some patients. Therefore, the

value of pre-operative data analysis would be limited. However, post-operative data were obtained from almost all patients and thus can be considered reliable.

In conclusion, an increase in bone turnover markers after surgery for hip fracture and the subsequent decrease may reflect bone formation and remodeling during the fracture healing process. We identified significant differences in bone formation and resorption marker levels between patients with trochanteric and femoral neck fractures, even though these both occur at adjacent sites in the proximal femur. Our findings may reflect differences in the amount of callus formation and/or remodeling during the healing of these fractures. After fragility fracture at different sites, the changes in bone turnover markers may show a similar pattern, but differ in extent.

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