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Original article

Changes in total alkaline phosphatase level after hip fracture: comparison between femoral neck and trochanter fractures

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Abstract

Background. Biochemical bone metabolic markers are affected by fractures, and total alkaline phosphatase (ALP) is considered one of the bone formation markers. Only a few reports have dealt with changes in bone formation markers during the healing process of bone fragility hip fractures. Despite the difference in the amount of callus formation and bone fusion rate, no significant differences in longitudinal change of total ALP between femoral neck and trochanter fracture have been reported.

Methods. A total of 69 osteoporotic patients with femoral neck or trochanter fracture whose serum concentrations of total ALP were examined at least four times at six periodic examination points (1, 2, 3, 4, 6, and 8 weeks after surgery) and whose state of bone union was obtained within 24 weeks after surgery were selected for this retrospective study. The characteristic longitudinal change of total ALP during the healing process was shown, and the possibility of total ALP as a predictive factor for the state of osteosynthesis of hip fractures is discussed.

Results. Changes in the total ALP level according to the healing process were similar for femoral neck and trochanter fractures. The concentration of total ALP rose to a maximum at 3 weeks after surgery and then gradually decreased for both fractures. However, the range of change was significantly greater for trochanter fractures than for femoral neck fractures. For trochanter fractures, total ALP decreased from 3 to 6 weeks after surgery in all but one patient.

Conclusions. Increases in the concentration of total ALP after surgery and the subsequent decreases may reflect the normal healing process. A significant difference in the changes of total ALP after surgery between femoral trochanter and neck fractures was shown. Periodic measurement of total ALP might be useful for obtaining information on the osteosynthesis state.

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Introduction

Osteoporosis, a common condition in elderly people, has been defined as "a skeletal disorder characterized by compromised bone strength predisposing a person to risk of fracture." Hip fracture, the most common type of bone fragility fracture, occurs in elderly patients with osteoporosis and causes serious and fatal problems. Delayed or non-union is a well recognized major and not rare problem of long bone fractures; it frequently occurs in cases of femoral neck fracture and is not rare in femoral trochanter fractures.

Recently we encountered three patients who had required a second surgery due to non-union of a trochanter fracture. Because of strong internal fixation, these patients could ambulate with light support. Two of the three patients complained of hip pain when they walked, whereas the remaining patient had no pain. In these cases, we detected no healing disturbance by plain radiography within a few months after surgery until cut-out or displacement of screws became evident. Delayed or non-union of a trochanter fracture without pain is not usual but may cause severe complications, such as displacement of screws. If there are any signs that reflect the status of osteosynthesis as well as radiographic evidence, more adequate and early treatment might be possible.

Bone turnover is initiated by osteoclasts, which erode the surface of old bone. Osteoblasts secrete new bone and fill the absorption cavity. Biochemical bone metabolic markers reflect these stages of bone turnover. Bone formation markers indicate osteoblast activity, and bone absorption markers indicate osteoclast activity. The healing process of a fracture may reflect those turnover markers.

Total and bone-specific alkaline phosphatase (ALP) assays are frequently used to monitor bone formation. Several studies[1–10] have shown that bone formation markers are affected by fractures and osteoporosis, and most of these markers have been described in relation to long-bone fractures. However, only a few reports have dealt with changes in bone formation markers during the healing process of bone fragility fractures.[2,7,10] Femoral neck fracture and trochanter fracture occurs in the adjacent part of the proximal femur and cause many serious problems in elderly patients. Despite the difference in the amount of callus formation and bone union rate, no significant differences in total ALP between femoral neck and trochanter fracture have been reported.[2]

We thought that these two fractures might be the most representative models of the effect of bone fragility fractures for bone turnover markers. We also suspected that the postoperative change in ALP activity between a femoral neck fracture and a trochanter fracture might be different because the amount of callus formation is clinically different. Furthermore, we speculated that measuring the changes in bone formation markers might help confirm bone union and predict the risk of delayed or non-union.

In this retrospective study, total ALP was selected as a bone formation marker following femoral neck and trochanter fractures. The characteristic pattern of change in total ALP levels during the healing process was shown, and the possibility of total ALP as a predictive factor for bony union of fractures in proximal femur is discussed.

Patients and methods

Surgical interventions for 240 cases of femoral neck or trochanter fracture were performed at our institution between January 2000 and December 2003. In principle, we prefer internal fixation methods for trochanter fractures; osteosynthesis using multiple pinning is used for all femoral neck fractures even when the fracture is type 3 or 4 according to Garden's classification.[11]

Patients with osteoporosis whose serum ALP concentrations were examined at least four times at six periodic examination points (1, 2, 3, 4, 6, and 8 weeks after surgery) and whose state of bone union was obtained up to 24 weeks after surgery were selected. The preoperative ALP value for selected patients was examined within 24 h after fracture.

Patients with major trauma such as a traffic accident were excluded from this study. The patients who were nonambulatory before or after the fracture due to other physical or mental conditions were excluded because their bone union could not be accurately assessed. We also excluded patients who had undergone unilateral hip replacement (UHR) due to a subcapital fracture or early displacement after multiple pinning for femoral neck fracture and patients who had undergone reoperation due to early displacement of the trochanter fracture. Six patients with femoral neck fracture had undergone a secondary UHR after the first multiple pinning due to early displacement, and three patients with trochanter fracture had undergone reoperation due to displacement within 3 weeks. The patients with malignant disease, liver disease, or any other fractures at the same time were also excluded.

Patients with trochanter fracture were usually allowed to start weight-bearing 3–6 weeks postoperatively and patients with femoral neck fracture usually 4–8 weeks after surgery. Thereafter, patients were encouraged to increase weight-bearing gradually.

At the end of the 24-week study period, all patients were assessed for clinical and radiological evidence of fracture healing. When radiologically discernible evidence of bridging callus, remodeling, or sclerotic change at the fracture site was judged by at least two independent orthopedic surgeons and the patient could walk without pain, we estimated that bone union was complete. If non-union became obvious within 24 weeks and the patient desired it, a second operation was performed.

Differences in the age and total ALP value at each examination point between femoral neck and trochanter fractures were assessed using Student's unpaired t-test. Statistical significance was set at a $P < 0.05$.

Results

Patients' backgrounds and overall results are shown in Table 1. A total of 69 patients were selected (57 women, 12 men). Their age range was 56–98 years (average 79.1 year). There were 30 patients (24 women, 6 men) with a neck fracture and 39 patients (33 women, 6 men) with a trochanter fracture. The average age for the former was 74.5 years and for the latter 82.7 years. The patients with a trochanter fracture were significantly older than those with a neck fracture. Preoperative values showed no significant differences between the two types of fracture.

All patients with femoral neck fracture were treated using multiple pinning, and patients with a trochanter fracture were treated using a captured hip screw (n = 28), Ender's nailing ($n = 6$), multiple pinning ($n = 3$), and γ-nailing ($n = 2$).

Figure 1 shows changes over time in the mean total ALP concentrations of patients with femoral neck and trochanter fractures. Total ALP had the same changing pattern, but the amount of change was significantly different. The trochanter fracture group showed a significant increase in the total ALP value than the femoral neck fracture group from 2 to 8 weeks after surgery.

Table 1. Alkaline phosphatase levels, by fracture type

Fracture	No. of patients	M/F	Age (years), mean and range	ALP level[a] (IU/l)		Increasing rate (%)
				Initial value	Peak value	
Trochanter	39	6/33	82.7 (59–98)	247.1 ± 68.9	478.1 ± 173.0	216.4 ± 75.6
Femoral neck	30	6/24	74.5 (56–93)	259.1 ± 78.4	331.4 ± 74.6	148.6 ± 22.8
*P***			0.0007*	0.4996	<0.0001	<0.0001

Results are the mean ± SD
* Patients with trochanter fractures were significantly older than those with neck fractures
** Unpaired *t*-test
[a] The normal value for total alkaline phosphatase (ALP) is 115–345 IU/l at our institution

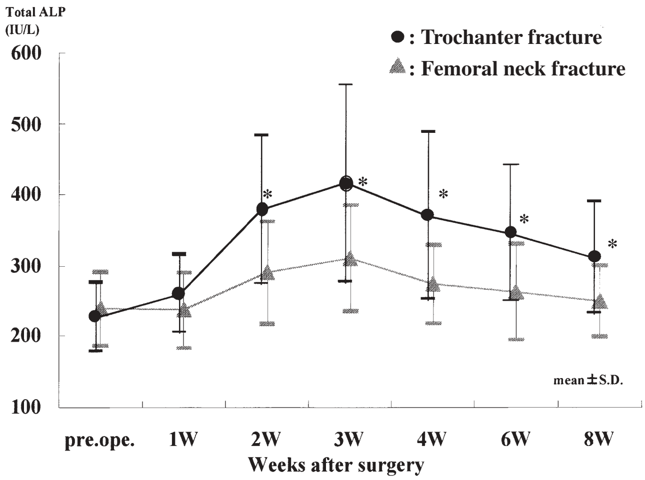

Fig. 1. Value of total alkaline phosphatase (*ALP*) after surgery. *The value for the trochanter fracture group is significantly higher than for the neck fracture group ($P < 0.05$)

In the trochanter fracture group, the concentration of total ALP rose after 1 week to reach a maximum within 3 weeks after surgery and then gradually decreased. The concentration in the trochanter fracture group had not returned to the initial level at 8 weeks after surgery, although the value had decreased from the peak level.

The ALP value at both 3 and 4 weeks after surgery was examined in 22 patients, and the value was decreased in 19 of 22 patients (86.4%) from 3 to 4 weeks. Furthermore, from 3 weeks to 6 weeks and from 3 weeks to 8 weeks after surgery, 17 of 18 (94.4%) patients and 21 of 22 (95.5%) patients showed decreased ALP values, respectively. In only one patient (a 59-year-old woman) did the total ALP value not decrease from 3 weeks to 6 weeks and from 3 weeks to 8 weeks after surgery (Table 2).

In the femoral neck fracture group, increases in the ALP concentration compared to the preoperative values were noted from 2 to 6 weeks after surgery; after the peak (at 3 weeks), the value decreased. The changing pattern of ALP in those with femoral neck fractures was almost same as that in those with trochanter fractures.

Table 2. Postoperative change of total ALP from 3 weeks after surgery in trochanter fracture patients

Weeks after surgery	No. of patients	ALP change (no. of patients)	
		Increase	Decrease
4	22	3 (13.6%)	19 (86.4%)
6	18	1[a] (5.6%)	17 (94.4%)
8	21	1[a] (4.5%)	21 (95.5%)

[a] Same patient (59-year-old woman)

Moreover, the amount of change was greater in the trochanter fracture group than in the femoral neck fracture group. The rate of maximum increase for the patients with preoperative values was significantly higher in the trochanter fracture group (femoral neck 148.6%; trochanter 216.4%) (Table 1).

During this study periods, three patients with trochanter fractures were estimated as having non-union, and two of the three underwent UHR, 13 weeks and 21 weeks after the initial surgery, respectively. The remaining patient underwent osteosynthesis again 9 weeks after initial surgery and attained bone union. Among these three non-union cases of trochanter fracture, two showed a different longitudinal change from the average pattern of normal union (i.e., continued hyper-activity or bimodal curve), and the remaining one showed hypoactivity (Fig. 2).

On the other hand, four patients with femoral neck fracture were deemed to have as non-union during the same period. However, we could not detect any valuable differences regarding the longitudinal change of ALP between normal union and non-union because the amount of change in the ALP concentration in the femoral neck fracture group with normal union was too small (Fig. 3).

Discussion

The process of fracture healing can be divided into three phases: inflammation, regeneration, remodeling.

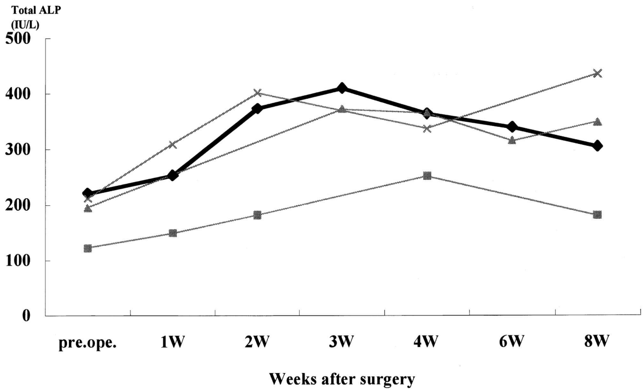

Fig. 2. Longitudinal change in total ALP in non-union cases of trochanter fracture. The *bold line* indicates the mean value of normal union trochanter fractures

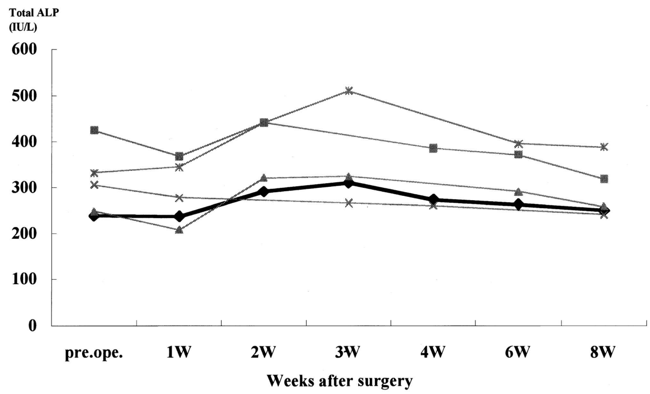

Fig. 3. Longitudinal change in total ALP in non-union cases of femoral neck fracture. The *bold line* indicates the mean values for normal union cases of femoral neck fracture

The changes in bone absorption and formation during the fracture healing process are thought to be more dynamic than the changes that occur during the physiological remodeling cycle. Biochemical bone metabolic markers reflect bone turnover. Correlation between these markers and bone formation and absorption has been demonstrated in normal subjects and in patients with osteoporosis.[12,13] Longitudinal changes in biochemical bone turnover markers after fracture have been reported, and several investigators have attempted to use these changes as indicators of delayed or non-union.[1–6,8–10,14] On the other hand, no one has reported on differences in the change of bone turnover markers for different fractures during the normal healing process.

Human serum contains a variable mixture of ALP isoenzymes from bone, liver, and intestine; and the total concentration represents the sum of the various effects of these isoenzymes. Most of the ALP isoenzymes derive from bone and liver,[15] and each accounts for nearly 50% of the total effect of all isoenzymes in each organ. The precise function of bone-specific ALP remains unknown, but this enzyme is thought to be involved in bone formation or mineralization, or both.[13,16]

Because total ALP is measured in many patients as part of routine examinations, we selected total ALP for monitoring bone healing in this retrospective study. We demonstrated the same longitudinal changing pattern of total ALP following osteosynthetic surgery of femoral neck and trochanter fractures and the difference in the increasing rate of total ALP between the two fractures after surgery.

Many authors[1–10] reported that bone specific or total ALP (or both) increased during the fracture-healing phase and continued at a high value long after the fracture. One study[5] that focused on bone-specific ALP following long-bone fractures found significant increases in isoenzyme activity during the healing phase. They reported that the maximum increase occurred between 8 and 12 weeks after fracture and returned to preinjury values after 24–30 weeks.

Hosking reported increased ALP activity after hip fracture and found no differences in the increases in total ALP levels between femoral neck and trochanter fractures.[2] Similar to Hosking's report, we found that the total ALP increased according to fracture healing for both hip fractures; on the other hand, unlike Hosking's report, the change according to time was significantly greater for the trochanter fracture than that for the femoral neck fracture. Radiographically, bone formation and remodeling of fracture healing was apparently greater for the trochanter fracture than for the femoral neck fracture. We thought that the differences in callus formation and remolding between these two fractures would reflect the difference of ALP activity, and our results might be reasonable with this radiographic evidence.

According to the results of our current study, we speculated that several types of fracture had characteristic changing patterns and amounts of bone turnover markers during the healing process. Usually, with a bone fragility hip fracture, postoperative total ALP activity rises to its peak value 3 weeks after surgery and then gradually decreases until 8 weeks after surgery. Especially for a trochanter fracture with normal bone union, only one female patient did not have decreased total ALP from 3 to 6 or 8 weeks after surgery (Table 2). With trochanter fractures, measuring total ALP activity at least three times (preoperation, 3 weeks after surgery, and 6 or 8 weeks after surgery) in association with radiological findings may be useful for monitoring the bone union process. When ALP shows the usual pattern (increasing for 3 weeks after surgery and then decreasing until 8 weeks after surgery), it may help to judge bony union. On the other hand, when ALP shows an unusual pattern, more careful observation and examination might be necessary especially when patients complain of unusual pain when walking. Three cases of non-union of a trochanter fracture were encountered in our study, although all of these patients could walk with or without hip pain. Two cases showed different longitudinal change from the normal union pattern (i.e., continued hyperactivity or a bimodal curve), and the remaining case showed hypoactivity (Fig. 2). However, this is just speculation because the number of cases of delayed union was too small to make any reliable comparisons.

In cases of femoral neck fracture, the range of increase in total ALP was too small, we were unable to reveal the difference in ALP variations between normal union and those with nonunion (Fig. 3).

Some patients with trochanter fracture can ambulate despite lack of bone union because of strong fixation by the surgical devices. Thus, any signs other than imaging studies seem to have little significant value for monitoring the process of healing even though the decision whether bone union has taken place cannot be made early after surgery. We propose here that it may be valuable to examine postoperative transition of the value of total ALP (before and 3, 6, and 8 weeks after surgery) to obtain information regarding the healing process after trochanter fracture but not for a neck fracture.

Even for total ALP, which is not a bone-specific metabolic marker, the difference in the amount of change after surgery between the femoral neck and trochanter fractures was significantly different. This result led us to further studies that use specific biochemical metabolic markers for both formation and absorption to obtain more accurate information about the fracture healing process. Bone-specific markers may be more suitable for evaluating the state of bony union than total ALP. However, because bone-specific turnover markers are difficult to use clinically and total ALP is widely accepted as a routine examination, it seems to be a more practical and useful clinical marker than any other bone-specific turnover marker.

Conclusions

We identified apparently significant differences in the changes in ALP concentrations after fracture of the femoral trochanter and neck fracture. Thus, biochemical monitoring of the fracture healing process using even total ALP may help judge bony union after trochanter fractures but not after femoral neck fractures.

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