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Review Article

Changes in Bone Turnover Markers and Fracture in Osteoporosis: A Review of the Literature

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Keywords

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Abstract

Osteoporosis is a worldwide condition primarily affecting the elderly. Bone fragility fractures that are due to osteoporosis, such as femoral proximal fracture and vertebral fracture, are increasing in Japan. The measurement of bone turnover markers greatly helps in the diagnosis and assessment of osteoporosis. Here, we review the relationship between bone fragility fractures and bone turnover markers through recent studies, including our own.

ABBREVIATIONS

BAP: Bone alkaline phosphatase, **NTX:** N-terminal telopeptide of type-I collagen, **IF:** Insufficiency fracture, **ORIF:** Open reduction internal fixation, **IR:** Increasing ratio, **DPD:** Deoxypyridinoline, **CTX:** C-terminal telopeptide of type-I collagen, **ICTP:** Cross-linked telopeptideof type-I collagen

INTRODUCTION

Osteoporosis is a worldwide condition that primarily affects the elderly. The estimated number of people with osteoporosis in Japan is 15 million, but only 20% receive treatment [1]. Bone strength generally reflects the integration of bone density and bone quality [2]. Thus, bone loss is a cardinal feature in osteoporosis, particularly in postmenopausal women [3].

Bone remodeling occurs throughout an individual's life. Impairment of bone remodeling, whereby bone resorption occurs predominantly over bone formation over an extended period, leads to osteoporosis. The rate of bone turnover can be assessed using biochemical markers. Specifically, several bone turnover markers have become more common of late these indicators greatly help in the diagnosis and assessment of osteoporosis [4].

Osteoporosis in the elderly was earlier thought to be a kind of low turnover condition in which bone metabolism was decreased [4]. However, we often experience unexpectedly high values of bone turnover markers in daily clinical practice. Elevated turnover markers were frequently observed in elderly people who also complained of lower back pain. Therefore, we earlier investigated the relationship among bone turnover markers, age, and lower back pain in patients with osteoporosis and found significant associations among these factors [5].

Based on the above findings, we next hypothesized that patients with vertebral fracture accompanying osteoporosis might have bone turnover acceleration and lower back pain. At the time of our clinical studies, few reports regarding bone fragility fractures and biochemical bone markers had been conducted. In the present review, we examine the relationship between bone fragility fractures and bone turnover markers through several ensuing studies, including our own [5-10].

SIDE HEADINGS/SUBHEADINGS

1. Does fracture affect bone metabolism markers?
2. Do bone metabolism markers change during the healing process of fractures?

① Changes in biochemical markers in the repair of femoral neck fracture

② Changes in ALP level in patients with proximal femoral fracture

③ Changes in other bone-specific markers in patients with proximal femoral fracture

④ Changes in biochemical markers in the repair of vertebral fracture

Wrist fracture

Ankle fracture

Tibia fracture

3. Summary of the literature

① Do changes in bone metabolism markers vary according to the type of fracture?

② Are there any differences in changes in bone metabolism markers for fractures excluding tibial fracture?

③ Are there any changes in bone metabolism markers values at fracture sites?

④ Until when do changes in bone metabolism markers continue after fracture?

4. Non-union and delayed union of fractures

5. Conclusion

DISCUSSION AND CONCLUSION

Does fracture affect bone metabolism markers?

We initially examined bone alkaline phosphatase (BAP) and urinary N-terminal telopeptide of type-I collagen (NTX) levels in patients with insufficiency fracture (IF), for which the differential diagnosis of bone metastasis is sometimes difficult. Indeed, since these bone turnover markers were remarkably high, we could not definitively diagnose bone metastasis in IF [6].

We next investigated the association between bone fragility fractures and cross-linked telopeptideof type-I collagen (ICTP), which has been considered to be a sensitive bone resorption marker in bone metastasis evaluation [7]. Along with other bone turnover markers, ICTP was significantly increased in elderly patients with bone fragility fracture [7]. These results suggested that fractures had substantial effects not only on ICTP, but also on several other biochemical markers.

Do bone turnover markers change during the healing process of fractures?

Changes in biochemical markers in the repair of femoral neck fracture: Fractures of the proximal femur are clinically classified as femoral neck fracture or trochanteric fracture, which occur at adjacent sites. Whereas bone healing is not easily achieved in the former fracture type, it is relatively obtainable in the latter. Therefore, we considered these fractures as good models to clarify the changes in biochemical bone markers during the healing process.

Hoesel *et al.* reported that urinary NTX was greater in trochanteric fracture than in femoral neck fracture as well as in hip fracture versus forearm fracture [8]. The authors stated that all cases of femoral neck fracture required total hip replacement [8]. Meanwhile, Yu-Yahiro *et al.* described in their study on bone turnover markers that 76% of subjects with femoral neck fracture underwent arthroplasty [9]. Although there are several reports describing the changes in bone metabolism markers between femoral neck fractures and trochanteric fracture [8,9], to the best of our knowledge, there are few data on the changes in bone turnover markers during the fracture healing process using open reduction internal fixation (ORIF) in patients with femoral neck fracture. As we had been employing ORIF in patients with femoral neck fracture [10], we conducted prospective and retrospective studies on subjects with femoral neck or trochanteric fracture with regard to changes in bone metabolism during the healing process.

Changes in alkaline phosphatase (ALP) level in patients with proximal femoral fracture: We investigated ALP level in patients with proximal femoral fracture before and after ORIF. Serum ALP values showed similar patterns in femoral neck and trochanteric fracture groups after surgery. In both groups, ALP rose at 2 weeks after surgery, peaked at 3 weeks, and then gradually decreased. The maximum ALP level in the trochanter fracture group was significantly higher than that in the femoral neck fracture group ($p<0.0001$). The rate of ALP increase in the trochanter fracture group (Increasing Ratio [IR]: 216.4%) was also significantly higher than that in the femoral neck fracture group (IR: 148.6%) [11].

Changes in other bone-specific markers in patients with proximal femoral fracture: Next, we performed a prospective study of patients with proximal femoral fracture to examine the values of serum BAP as a bone formation marker and urinary deoxypyridinoline (DPD), serum and urinary NTX, and urinary C-terminal telopeptide of type-I collagen (CTX) as bone resorption markers. BAP was decreased at 1 week after surgery, then increased and peaked at 3 weeks post-operatively. On the other hand, all of the bone resorption markers increased immediately after surgery: urinary NTX peaked at 3 weeks, serum NTX peaked at 3-5 weeks, urinary DPD peaked at 5 weeks, and urinary CTX peaked at 2-3 weeks after surgery. We observed that results varied with respect to urinary and serum NTX [12].

Taken together, we witnessed that bone formation markers and bone resorption markers showed similar patterns in patients with trochanter fracture or femoral neck fracture. However, all of the markers peaked at significantly higher values in patients with trochanter fracture.

Changes in bone turnover markers in the repair of vertebral fracture: In our previous study on vertebral fracture, serum BAP soon increased and peaked (IR: 148%) at 3 weeks after injury. The maximum value was significantly higher than that of the baseline. Although BAP began to decrease at 3 weeks, it maintained a markedly high value (IR: 120%) until 8 weeks. Urinary NTX also increased right after the injury, peaked at 3 weeks (IR: 179%) at a significantly higher value, and maintained this significant difference until 8 weeks (IR: 148%). In addition, our results revealed a negative correlation between bed rest period and peak BAP value ($r=-0.340$, $p=0.03$), but no association was seen for bed rest and urinary NTX [13].

According to Ohishi *et al.*, urinary and serum CTX peaked at 4 weeks and 2 weeks, respectively, and both decreased thereafter. On the other hand, OC reached its maximum at 24 weeks and maintained a high value, even at 48 weeks [14].

Changes in bone turnover markers for other fractures:

Wrist fracture: In their examination of 20 cases, Ingle *et al.* reported that BAP peaked at 2-4 weeks after injury and IR was

20-24% compared with values obtained right after the fracture. OC peaked at 26 weeks, and P1NP peaked at 6 weeks with an IR of 55%, which was a marked increase. OC and P1NP remained at high values even at 52 weeks (IR: 20%) after the fracture. On the other hand, the peak IR of urinary DPD and urinary NTX was not significant at 18% and 35%, respectively, at 6 weeks. These markers had returned to baseline levels at 52 weeks [15].

Ankle fracture: Ingle *et al.* also described that in ankle fracture, bone formation markers that include serum BAP, P1NP, and OC increased significantly between 1 to 4 weeks after injury by 11-78%. While BAP had returned to a baseline level at 52 weeks, PINP and OC remained elevated. The bone resorption markers serum TRAP-5b and urinary DPD remained elevated at 52 weeks, but NT had decreased [16].

Tibia fracture: Veitch *et al.* reported that serum CTX increased within 3 days after tibial fracture, peaked at 2 weeks (IR: 139%), and maintained a higher value at 24 weeks (IR: 105%). On the other hand, BAP peaked at 24 weeks (IR: 199%) and decreased gradually thereafter, but remained elevated at 1 year after the fracture. OC also peaked at 24 weeks. However, the marker's IR was 33%, which was comparatively lower than that of the other markers [17].

SUMMARY OF THE LITERATURE

Are there any differences in bone turnover markers according to fracture type?

In most fractures, bone resorption markers and BAP increased at an early stage, peaked after several weeks, and then decreased. Only in tibial fracture, serum CTX increased within 2 weeks and remained elevated for over a year after the injury. Furthermore, BAP peaked at a later stage at approximately 24 weeks. These results suggest that most tibia fractures mainly involve solid cortical bone, as compared with other types of bone fracture that affect mostly cancellous bone.

Are there any differences in bone turnover marker changes in fractures excluding tibia fracture?

When comparing femoral neck and trochanteric fractures, bone turnover markers showed specific patterns for each fracture group, even for urinary and serum NTX. Turnover markers displayed similar patterns for both fractures. For vertebral fracture, peak urine CTX was different from that of serum CTX. Bone absorption markers increased and peaked at several weeks after the fracture. Bone turnover markers also showed specific expression patterns after this injury type.

We noted that BAP increased at an early stage. In contrast, the increase in OC was delayed but persisted for a long period after the injury. The results presented in this review confirm the notion that BAP increases in the early stages following fracture and that OC is expressed at a more mature period of bone formation.

Are there any changes in bone turnover marker values at fracture sites?

In femoral neck and trochanteric fractures, the changes in bone turnover markers showed similar patterns, although those for the latter fracture type were significantly higher. The increased rate of bone turnover markers in ankle or wrist fracture was significantly lower than that in femoral neck fracture or vertebral compression fracture. With regard to IF, marker values were greatly increased; the average peak values of BAP and NTX were 87.9 mmol Cr/L and 201.3 mmol Cr/L, respectively. These results suggest that the size of the bone affects the values of bone turnover markers in fractures.

Until when do changes in bone turnover markers continue after fractures?

In vertebral, ankle, and wrist fractures, bone metabolism markers apart from OC returned to baseline levels within 1 year. In contrast, bone resorption markers returned to baseline values at 6 months for hip fracture, and bone formation markers including BAP and OC were elevated even after 1 year.

It appears that the effects of fracture on bone resorption markers vanish within a year after injury. In many cases, however, bone formation markers, such as OC and P1NP, remain high for 1 year and longer. These findings indicate that bone fracture repair is in fact a lengthy process. Accordingly, bone turnover marker monitoring for at least 1 year is recommended for bone fragility fractures.

Non-union and delayed union of fractures

Our earlier study has showed that the diagnosis of delayed- or non-union fracture using biochemical markers is challenging [11]. Ohishi *et al.* reported that levels of bone formation markers including OC were lower in a delayed union group than in a normally united group [14]. Cox *et al.* comprehensively reviewed the changes in biochemical markers in fracture healing. They describe that there is no consensus with respect to the association between the changes in bone turnover markers and the healing of delayed- or non-union fracture [18].

CONCLUSIONS

1) Bone turnover markers show dynamic variations during the bone fracture healing process; 2) The expression change of each marker is different; 3) The amount of change of each marker varies by fracture site; 4) The change in each marker is affected by the degree of fracture; and 5) At present, it remains challenging to diagnose fracture non-union using bone metabolism markers.

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