REVIEW

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The role of antiosteoporotic drugs in fracture healing

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ABSTRACT

This narrative review was carried out to investigate the effect of antiosteoporotic drugs (selective estrogen receptor modulators [SERMs], bisphosphonates, denosumab, teriparatide, romosozumab) in fracture healing process of vertebral, hip and distal radius fractures. The administration of bisphosphonates (BPs) didn't affect the fracture healing process and clinical results after distal radius and hip fractures. However, there no evidence for vertebral fractures. Denosumab doesn't seem to delay the process of fracture healing in patients with non-vertebral fractures in a study that was well documented and designed. There no human studies that appreciated the influence of SERMs and romosozumab in fracture healing process. In one study was reported that patients with distal radius fractures who were treated with teriparatide had shorter time of fracture healing, however this was not clinically significant. On one hand, in hip fractures, some recent studies suggested that in patients treated with teriparatide there was better improvement of pain and clinical outcomes of functionality. On the other hand, in vertebral fractures, there was no statistically significantly difference regarding the stability of fractures between teriparatide and control groups. Considering the fact that there is no evidence that antiosteoprotic drugs influence negatively the fracture healing, there is no reason to delay the initiation of antiosteoporotic treatment after the fracture.

KEYWORDS: bisphosphonates, denosumab, fracture healing, osteoporotic fractures, teriparatide

Introduction

The aim of anti-osteoporotic drugs is to prevent osteoporotic fractures (vertebral, hip, distal radius, humeral neck fractures etc.). Despite the fact, that diagnosis of osteoporosis is easy and there are a lot of anti-osteoporotic drugs available for prescription, evaluations and treatments of osteoporosis have not been adequately implemented [1]. This fact is called "care gap" and patients with a recent osteoporotic fracture are the therapeutic target group in order to decrease this gap in treatment [2,3]. In order to achieve the correct management of these patients, it is very important to understand how anti-osteoporotic drugs affect the healing of fractures.

Fracture healing is a complex procedure consisting of cellular interaction and new bone formation [4,5]. Delayed fracture healing or nonunion of fractures is a complicated issue which decisively influ-

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ences the healing of fractures; when fracture healing is not achieved within six months we are talking about delayed union, while when fracture union has been late for over nine months it's about non-union [6].

Consequently, the purpose of this narrative review is to investigate how antiosteoporotic drugs affect the process of fracture healing.

Selective Estrogen Receptive Modulators (SERMs)

It is known that selective estrogen receptive modulators combine the advantages of estrogen in skeletal tissue without negative consequences in other organs [7]. In an in vitro study by Taranta et al [8], raloxifene which is the main representative of SERMs used in treatment of osteoporosis, contributed to the reduction of bone remodeling rate, and was instrumental in the weakening of osteoclastic activity while at the same time contributed to the preservation of osteoblast activity. In an ovariectomized rat study by Cao et al [9], both estrogens and raloxifene suppress to a mild degree hard callus remodeling and don't prevent the progress of fracture healing. In another two studies using mice, estrogen and raloxifene contributed to the creation of fracture callus with larger areas of chondrocytes, increased thickness of trabecular bone, reduced fracture healing time in comparison with controls [10,11]. These findings were seen in both the metaphysis and diaphysis of the bones. Despite of these, there no human studies assessing the effect of estrogen or raloxifene on fracture healing.

Bisphosphonates

Bisphosphonates (BPs), which are first line treatment for osteoporosis [12], act by inhibiting osteoclast activity [13]. BPs adhere to the hydroxyapatite binding sites on the surface of the bone, in particular active bone resorption surfaces. Consequently, there is concern that BPs may affect fracture healing or may have adverse effects on functional rehabilitation after fracture [14].Contrary to concerns, a satisfactory number of animal studies suggest that bisphosphonates are primarily remained to the point of the acute fracture site. On the one hand, bisphosphonates increase callus formation which contributes to mechanical functionality and stability, but on the other hand inhibit remodeling of the bone by modifying the morphology of callus [15]. Regarding the time of administration of bisphosphonates, the delayed for 1-2 weeks single intravenous administration of zoledronic acid contributes to the increase in the size and strength of the callus formation and at the same time improves mechanical properties of hard callus compared to weekly bisphosphonates [16,17]. These findings support that the single intravenous administration of zoledronic acid contributes to the production of larger and stronger hard callus [15].

The effect of bisphosphonates on fracture healing of the wrist has been studied since the beginning of 2000. Among the antiosteoporotic drugs, bisphosphonates have been studied the most so far [18]. A randomized controlled study by van der Poest Clement et al [19], which compared patients with distal radius fracture who received alendronate versus placebo, argued that there was no statistically significant difference between the two groups in fracture healing rate. Moreover, the group of patients who took alendronate showed an increase in bone mass. Furthermore, two studies from the same group patients compared patients receiving bisphosphonates with patients who had not received bisphosphonates and suffered from a distal radius fracture which was treated conservatively. In the studies no statistically, significant differences were found between the two groups regarding the healing time of the fractures and the clinical or functional results [20, 21].

Two other studies assessed the effect of the timing of alendronate administration on fracture union of distal radius fractures which were treated with open reduction and internal fixation and concluded that early administration of alendronate does not affect radiological or clinical results [22,23]. A multicenter randomized placebo-control trial was recently conducted in the United Kingdom in an effort to assess the effect of weekly alendronate in the treatment of fractures of the distal radius. The researchers administered alendronate 70mg on a weekly basis, fourteen days after a distal radius

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fracture that was treated either conservatively or surgically. They concluded that the administration of alendronate in an early stage does not disadvantage fracture healing or clinical results [24].

In hip fracture patients, treatment with bisphosphonates showed decrease in biochemical markers of bone metabolism and anti-resorptive impact. In a study by Altintas et al [25], was supported that at the end of three months of risedronate treatment, a significant decrease in urinary N-telopeptide levels was observed. Furthermore, Cecilia et al [26], suggested that treatment with alendronate caused an increase in bone mineral density in proximal femur and a decrease in biochemical markers of bone metabolism. In a large multicenter study, a single intravenous administration of zoledronic acid in the first trimester after a hip fracture was not related with a remarkable delay in fracture union [27]. In another trial by Kim et al [28], the administration of risedronate at an early stage did not affect results of functionality and complication rate in patients with intertrochanteric fractures who treated surgically as in patients with distal radius fractures who were treated with operation. Despite of this, in a recent trial by Lim et al [29], was suggested that history of bisphosphonate administration was associated with an increased risk of delayed fracture healing at 3 months in patients with intertrochanteric fractures who were treated surgically.

The effect of bisphosphonates on vertebral fracture healing has not yet been adequately evaluated. In a prospective trial by Ha et al [30], current use of bisphosphonates did not affect clinical results to a significant extent. However, patients receiving bisphosphonates developed intervertebral fissures which could be an indicative factor of affected healing of osteoporotic vertebral fractures.

Denosumab

Denosumab is a strong inhibitor of bone resorption caused by osteoclasts, and is believed to have similar properties to bisphosphonates as far as the healing of the fractures [31]. As with bisphosphonates, denosumab does not seem to affect facture healing in experimental animal studies [15]. In denosumab treated animals, the volume of hard callus was raised at the fracture site and bone remodeling was delayed. Furthermore, in experimental animal studies with mouse femurs has been suggested that denosumab increases torsional stiffness [32].

Apart from the FREEDOM study data, there are few published clinical results involving fracture healing in patients treated with denosumab. In this large multicenter trial, 7808 postmenopausal women were randomized to receive either denosumab or placebo and 667 patients had sustained 851 non-vertebral fractures (e.g. hip fractures, humeral head fractures, distal radius fractures etc.) during the entire time period. In any person who had received denosumab six weeks before or after the fracture, delayed union or nonunion of the fracture was not observed. There was no statistically significant difference between the denosumab group and the placebo group in relation to the complication rates that were associated with the fracture or the intervention. The researchers concluded that denosumab does not delay fracture healing or play any role in causing complications even when given the time period around the fracture [33].

Teriparatide

Teriparatide is a powerful anabolic agent that contributes to the increase of bone mineral density (BMD) in patients suffering from severe osteoporosis. PTH contributes to increasing the activity and lifespan of osteoblasts and has as a consequence increased bone formation on all bone surfaces [34,35]. In addition, it contributes to the increase of connectivity of the trabecular bone as well as in the increase in thickness of cortical bone which strengthens the biomechanical properties of the bone [15]. In another animal study by Kakar et al [36], was suggested that teriparatide increases recruitment and differentiation of chondrocytes which are basic processes endochondral ossification at an early stage. Therefore, teriparatide affects both cartilage and mineralized callus formation in the process of healing of the fractures [37]. Regarding the timing of teriparatide administration, its early dosing within a week after the fracture, is associated with better fracture healing [38, 39].

In a clinical study by Aspenberg et al [40], was

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supported that teriparatide appears to contribute to callus formation after distal radius fracutres. Anyway, the effect of teriparatide in healing of the distal radius fractures has not yet been well estimated [41]. Only one randomized prospective multicenter study seems to suggest that in patients with conservatively treated distal radius fractures, to whom teriparatide was given, had a better average time of union (about one to two weeks) compared with controls. Despite of these, there was not statistically significant difference between the two groups concerning improvement of pain and scores of functionalities [42].

The effect of teriparatide on hip fracture healing is unclear. In a randomized placebo-control trial by Bhandari et al [43] in patients with femoral neck fractures who were surgically treated with internal fixation, there was no statistically significant difference regarding the proportion of patients whose fractures were united or they needed revision surgery between the patients who received teriparatide compared with controls. Moreover, the administration of teriparatide didn't improve the radiological signs of fracture union neither reduce pain compared with controls. Anyway, two retrospective studies supported findings that contradict previous study. In a trial by Huang et al [44], was reported that patients received teriparatide after surgical stabilization for intertrochanteric fractures had significant improvement in pain and better quality of life. In another trial by Kim et al [45], was supported that in patients with unstable intertrochanteric fractures who were surgically treated with proximal femoral nail fixation, in patients treated with teriparatide in comparison with controls, the time to fracture healing, relief of pain and improvement of scores of functionalities were better.

The effect of teriparatide on osteoporotic fractures of the spine is controversial. In a trial by Tsuchie et al [46], there was statistically significant difference regarding the collapse of vertebral body and the change of kyphotic angle in patients with fractures of thoracolumbar spine who were treated with teriparatide. However, in another two studies was not reported statistically significant difference regarding these parameters of stability between the two groups [47,48].

Romosozumab

Romosozumab is an antibody that targets sclerostin, is a contemporary new treatment option and its target group is elderly women with severe osteoporosis. In a study by Takase et al [49], was supported that in fractures of ovariectomized rats, romosozumab and active vitamin D_3 increased trabecular bone volume, but they didn't accelerate the fracture healing process. The influence of romosozumab on fracture healing remains controversial and further trials must investigate the expression of sclerostin during the early and late phases of fracture healing.

Comparisons between drugs

The comparison of the role of teriparatide in fracture healing compared to other drugs such as bisphosphonates resulted from recent very widespread use of teriparatide in osteoporotic fractures. In a double-blind clinical study by Aspenberg et al [50], patients with trans- trochanteric femoral fractures who were treated with internal fixation, received either teriparatide or risedronate. The administration of teriparatide in comparison with risedronate was related to less pain and shorter time to complete the Timed Up-and-Go test in the time interval between six and twenty-six weeks. Despite of these, other clinical outcomes associated with rehabilitation after fracture, such as union rate of the fracture, time until fracture healing, scores of the physical function were similar between the two groups.

Most comparisons between teriparatide and bisphosphonates were conducted in patients with osteoporotic vertebral fractures. On one hand, in a trial by Tscuchie et al [46], was supported that in patients treated with teriparatide, less change in kyphotic angle and less vertebral body collapse were observed. On the other hand, Iwata et al [51], suggested that the stability parameters in fracture site were similar to a significant extent between the two groups. Furthermore, in a trial by Min et al [48], was mentioned that the height loss of vertebral body was less in teriparatide-treated patients while there was not statistically significant difference regarding the rate of fracture instability and

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local kyphosis change between the two groups. In reference to the pain at fracture site, two studies supported that in patients treated with teriparatide there was less pain to a significant extent at last follow-up [46, 48]. In another trial by Kang et al, was reported that patients treated with teriparatide had less pain, but the clinical data were not different to a statistically significant extent [52]. Finally, in a trial by Hanji et al was suggested that clinical data related to pain were recorded according to pain assessment methods [53].

Conclusions

The administration of bisphosphonates does not affect the process of the facture healing after vertebral, hip and distal radius fractures. Despite the fact that clinical evidence is incomplete, denosumab does not appear to delay the healing process of non-vertebral fractures. In relation to the effect of SERMs and romosozumab on the process of fracture healing, there are no human studies. The administration of teriparatide in patients with distal radius fractures showed shorter healing time, while in patients with hip fractures, the healing time was unclear but was suggested that patients had minor pain and better clinical results in scores of functionalities. In patients with vertebral fractures, there were no evidence of clinical data that teriparatide shortens the healing time of fractures but was supported that there was greater improvement in pain at the fracture site. Considering the fact, that there is no evidence that antiresorptive drugs delay the healing of the fracture process and the fact that after the first osteoporotic fracture, the risk of subsequent osteoporotic fracture is particularly increased, there is no reason to delay the initiation of antiosteoporotic treatment after the fracture. Anyway, high-quality randomized controlled studies are needed to investigate further the role of antiosteoporotic drugs in fracture healing.

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