Osteoporos Int
DOI 10.1007/s00198-015-3331-7

REVIEW

Effect of osteoporosis medications on fracture healing

V. Hegde[1] · J. E. Jo[2,4,5] · P. Andreopoulou[3] · J. M. Lane[4]

Received: 2 July 2014 / Accepted: 17 September 2015

Abstract Antiosteoporotic medications are often used to concurrently treat a patient's fragility fractures and underlying osteoporosis. This review evaluates the existing literature from animal and clinical models to determine these drugs' effects on fracture healing. The data suggest that these medications may enhance bone healing, yet more thorough prospective studies are warranted. Pharmacologic agents that influence bone remodeling are an essential component of osteoporosis management. Because many patients are first diagnosed with osteoporosis when presenting with a fragility fracture, it is critical to understand how osteoporotic medications influence fracture healing. Vitamin D and its analogs are essential for the mineralization of the callus and may also play a role in callus formation and remodeling that enhances biomechanical strength. In animal models, antiresorptive medications, including bisphosphonates, denosumab, calcitonin, estrogen, and raloxifene, do not impede endochondral fracture healing but may delay repair due to impaired remodeling. Although bisphosphonates and denosumab delay callus remodeling, they increase callus volume and result in unaltered biomechanical properties. Calcitonin increases cartilage formation and callus maturation, resulting in improved biomechanical properties. Parathyroid hormone, an anabolic agent, has demonstrated promise in animal models, resulting in accelerated healing with increased callus volume and density, more rapid remodeling to mature bone, and improved biomechanical properties. Clinical data with parathyroid hormone have demonstrated enhanced healing in distal radius and pelvic fractures as well as postoperatively following spine surgery. Strontium ranelate, which may have both antiresorptive and anabolic properties, affects fracture healing differently in normal and osteoporotic bone. While there is no effect in normal bone, in osteoporotic bone, strontium ranelate increases callus bone formation, maturity, and mineralization; forms greater and denser trabeculae; and improves biomechanical properties. Further clinical studies with these medications are needed to fully understand their effects on fracture healing in order to simultaneously treat fragility fractures and underlying osteoporosis.

Keywords Fracture healing · Medication · Osteoporosis · Pharmacology

✉ J. E. Jo
jonathan.e.jo@gmail.com

[1] Department of Orthopaedic Surgery, University of California Los Angeles, 100 UCLA Medical Plaza, Suite 755, Los Angeles, CA 90095, USA

[2] Weill Cornell Medical College, 445 E 69th St, New York, NY 10021, USA

[3] Department of Endocrinology, Hospital for Special Surgery, 519 East 72nd St, Suite 202, New York, NY 10021, USA

[4] Department of Orthopaedic Surgery, Hospital for Special Surgery, 475 East 72nd Street, Ground Floor, New York, NY 10021, USA

[5] 2900 Main St. Apt 332, Bridgeport, CT 06606, USA

Introduction

The initial diagnosis of osteoporosis commonly occurs when a patient presents with a fragility fracture [1, 2]. To appropriately manage both the fracture and osteoporosis, it is essential to understand how osteoporosis medications influence fracture healing. In general, these agents counteract bone loss by inhibiting bone resorption or promoting bone formation. Thus, osteoporotic medications are split into two major categories: the antiresorptive medications, consisting of bisphosphonates, denosumab, calcitonin, estrogen, and selective estrogen

Published online: 29 September 2015

receptor modulators (SERMs), and the anabolic agents, which include parathyroid hormone (PTH) analogs and strontium ranelate (SR). Since remodeling is crucial to fracture healing, both classes of drugs have the potential to hinder or accelerate this process. In addition to these agents, supplements such as calcium and vitamin D are integral to bone health and may impact healing. This is particularly true in osteoporosis, which has been identified as a risk factor for impaired fracture healing. Animal studies have shown that osteoporosis can cause a significant reduction in fracture callus size, bone mineral density (BMD), and mechanical strength [3]. Histomorphologically, new bone trabeculae in osteoporotic models are arranged in a loose and irregular fashion, demonstrating the poor quality of the new bone formed [4].

This review will describe how these drugs alter bone metabolism and will explore existing data on how they influence fracture healing. An exhaustive literature search was undertaken in PubMed, and English language articles were selected that examined each chosen osteoporotic medication in the context of fracture healing. Titles and abstracts were screened to determine if they contained information pertaining to the subject of the review. If so, the full article was read before including it in the manuscript. No articles were excluded based on their results. Despite recent interest in newer antiosteoporosis medications such as antisclerostin antibodies and cathepsin K inhibitors, reporting on their role in fracture healing would be premature due to limited and incomplete preclinical data [5–8]. Studies are ongoing, but these drugs will not be included in this review. A list of included drugs and summaries of animal and clinical evidence are provided in Tables 1 and 2.

Calcium and vitamin D

Overview

Calcium and vitamin D management is critical for osteoporotic patients, as deficiencies have been identified as a common underlying finding in patients with fragility fractures. Calcium is one of the major constituents of bone, and vitamin D has been shown to play an important role in maintaining calcium homeostasis, improving muscle function and preventing falls [1, 9, 10]. Together they have been shown to reduce fractures among the elderly.

Animal studies

Most animal studies examining the role of vitamin D have shown a positive effect on fracture healing [11–14]. In animal models, the plasma concentration of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), one of the active vitamin D metabolites, rapidly decreases following a fracture. This rapid reduction is not a result of systemic decreased synthesis or increased degradation, but of increased consumption. In fact, $1,25(OH)_2D_3$ may localize to the callus and regulate the healing process [15, 16]. The other active metabolite, 24R,25-dihydroxyvitamin D_3 ($24R,24(OH)_2D_3$), may also have a key role in fracture healing. In a chick model, tibial fractures had inferior healing and bone mechanics when treated only with $1,25(OH)_2D_3$ compared to those treated with both $1,25(OH)_2D_3$ and 24R, $24(OH)_2D_3$ [17]. Furthermore, $24R,24(OH)_2D_3$-specific receptors have been identified in the healing callus and endochondral chondrocytes of animal models, suggesting the metabolite's specific role in fracture healing [18–20].

Mechanistically, the active metabolites of vitamin D act to increase new bone volume, callus volume and density, and trabecular number at the fracture site through various means. $1,25(OH)_2D_3$ promotes osteogenic differentiation during early osteoblastogenesis and directly stimulates mineralization of the extracellular matrix through activation of osteoblast vitamin D receptors [21–24]. This mineralization is also enhanced by the catabolic products of $1,25(OH)_2D_3$ and 25(OH)D (1, $24R,25(OH)_3D_3$ and $24R,25(OH)_2D_3$, respectively). In addition, biomechanical parameters show improvement in ultimate load at failure and energy absorption. This improvement in mechanical properties is closely associated with an increase in the total amount of enzymatic collagen cross-links in the callus [20]. An increase in the transformation of woven bone into lamellar bone also takes place, resulting in improved callus remodeling compared to controls [25]. This improved remodeling may be attributable to a theorized role for vitamin D as a regulator of osteoclastogenesis, based on the expression of vitamin D receptors by osteoclasts and the fact that 1, $25(OH)_2D_3$ stimulates osteoclast formation from bone marrow cells [26–29].

Clinical evidence

Clinical studies, although limited, also support the positive effect of calcium and vitamin D supplementation on fracture healing. In the only randomized, double-blinded, placebo-controlled study reported in the literature, 30 previously untreated women with proximal humerus fractures were either given calcium and vitamin D supplementation or placebo. The primary outcome measure was the difference in BMD at the fracture site. At 6 weeks, BMD was significantly higher in the treated group, indicating a positive impact of vitamin D and calcium supplementation on fracture healing [30]. Further support for the role of vitamin D in fracture healing comes from the study of nonunion by Brinker et al. After eliminating poor instrumentation and osteomyelitis, 84 % of patients (31 out of 37) with nonunion were found to have metabolic or endocrine abnormalities. Of these patients, 81 % (25 out of 31) had vitamin D deficiency [31]. Although controversy exists in the literature as to the true definition of vitamin D

Table 1 Summary of animal studies

Agent	Class	Animal study summary
Vitamin D	Supplemental	– Undetermined effect on healing rate – Increased callus volume and density – Enhanced mechanical properties
Bisphosphonates	Antiresorptive	– Delayed rate of callus maturation following cartilage calcification; rate of initial callus formation unaffected – Increased callus volume and bone mineral content – Enhanced mechanical properties
Denosumab	Antiresorptive	– Delayed callus remodeling – Increased callus volume and bone mineral content – Enhanced load-carrying capacity and torsional rigidity
Calcitonin	Antiresorptive	– Increased early endochondral ossification/cartilaginous healing – Greater cartilaginous callus maturation, no effect on callus volume – Enhanced load-carrying capacity and torsional rigidity
Estrogen and selective estrogen receptor modulators	Antiresorptive	– Suppressed callus remodeling but no effect on overall rate of fracture repair – Increased callus formation, trabecular density, mineralization, and neocortical thickness – Enhanced force to failure and stiffness
Parathyroid hormone	Anabolic	– Augments early endochondral repair – Increased callus volume, density, and maturity – Enhanced torsional strength and stiffness
Strontium ranelate	Anabolic	– Increased early osteogenesis – Increased callus volume and bone mineral density in osteoporotic bone – Enhanced callus stiffness and ultimate load

deficiency, in this study, it was set to a D25(OH) less than 30 ng/mL or a D1,25$(OH)_2$ less than 25 pg/mL.

Although there is favorable evidence of calcium's effects on fracture healing, there is concern about its safety. One randomized controlled trial and reviews of other large clinical trials suggest an association between calcium supplementation and cardiovascular events [32, 33]. Many of the studies involved elderly women, a population that constitutes the majority of osteoporotic patients. Yet other studies have shown no effect of calcium supplementation on the rate of cardiac events, making this observation controversial. Nevertheless, it is important to keep in mind that calcium supplementation may not be inconsequential in fracture healing or osteoporosis management, particularly in elderly women with cardiovascular comorbidities. Serum levels of intact PTH may be monitored with a target of 20–40 pg/mL to ensure sufficient calcium and vitamin D intake, and prevent potential oversupplementation that may lead to increased cardiac risk [34, 35].

Antiresorptive agents

Bisphosphonates

Overview

Bisphosphonates are popular antiresorptive agents used in treating osteoporosis. They have been proven to reduce fractures, improve BMD, and normalize elevated serum bone markers. Bisphosphonates are specifically drawn to bone due to their chemical structure and are taken up by local osteoclasts [36]. They target these cells and slow bone remodeling by inhibiting their resorptive actions and inducing their apoptosis. The antifracture efficacy of bisphosphonates has been well documented: according to the Fracture Risk Intervention Trial, alendronate reduced the risk of vertebral fracture and hip fracture by over 70 and 50 %, respectively [1, 37].

Animal studies

Several studies have examined fracture healing in bisphosphonate-treated animals. These studies show that for fractures healing by endochondral ossification, bisphosphonates preferentially deposit at the acute fracture site and are able to increase callus and trabecular bone volume, as well as bone mineral content (BMC) during the reparative phase of bone healing [38–40]. This is offset by a delay in the callus maturation to lamellar bone and remodeling to compact bone once calcified cartilage is formed. The initiation of callus formation, on the other hand, appears unaffected. Compared to controls, this larger, less mature callus has superior biomechanical properties [41, 42]. Mechanical functioning is maintained despite the inhibited bone remodeling by a compensatory modulation in callus morphology. This is in contrast to fracture healing via intramembranous ossification, a process in which biomechanical strength is more reliant on remodeling of trabecular bone.

Table 2 Summary of clinical evidence

Agent	Class	Clinical evidence	Quality of evidence[a]
Calcium/vitamin D	Supplemental	May increase bone mineral density at fracture site	Weak
Bisphosphonates	Antiresorptive	Does not delay healing May increase BMD at fracture site when given 2 weeks after fracture	Moderate
Denosumab	Antiresorptive	Does not delay healing Does not contribute to other complications	Weak
Calcitonin	Antiresorptive	May accelerate fusion May shorten time to mobilization (mixed results)	Weak
Estrogen/selective estrogen receptor modulators	Antiresorptive	No clinical evidence	Weak
Parathyroid hormone	Anabolic	May accelerate healing in hip, distal radius, and spine fractures	Moderate
Strontium ranelate	Anabolic	May facilitate fusion after delayed union or nonunion	Weak

[a] Quality of clinical evidence was classified as weak, moderate, or strong based on the level of evidence of existing literature. A "weak" rating consisted of mainly level 3–4 studies or a single level 2. "Moderate" indicated multiple level 2 studies or conflicting level 1 data. "Strong" evidence consisted of multiple level 1 studies with generally consistent findings

The literature on the use of bisphosphonates to improve implant fixation also has important implications for their effect on the healing of cancellous bone. Animal studies on the systemic delivery of bisphosphonates have shown improved bone-implant contact, peri-implant bone volume, and implant fixation strength, all of which are important endpoints that are indicative of increased implant stability [43–50]. Local delivery through binding the bisphosphonate to coatings on the implant surface has also shown improved implant stability, although local delivery has been shown to be less effective in a direct comparison [48, 51–53]. The effectiveness of bisphosphonates in improving implant stability is likely due to an antiresorptive effect similar to the effect on shaft callus: bone volume and, consequently, bone-implant contact and fixation strength are increased, but remodeling into mature lamellar bone is inhibited.

The effect of bisphosphonates on endochondral ossification suggests that the size and strength of the callus can be controlled by regulating bone remodeling during the healing process. Consequently, the timing and dosing regimen of bisphosphonate administration postfracture may have a significant impact on callus properties. In a rat model, bolus single-dose zoledronic acid was administered either at the time of, 1 week after, or 2 weeks after a fracture and compared with a saline control. Evaluation at 6 weeks postfracture showed that the delayed 2-week administration yielded the callus with the greatest size and strength [40, 54]. Furthermore, this single-dose bolus method yielded superior mechanical properties compared to weekly dosing [38]. Therefore, delayed administration of bolus-dosed bisphosphonates may be optimal to target the fracture site after the initial anabolic fracture response and generate a larger, stronger callus.

Clinical evidence

Clinical studies evaluating the effect of bisphosphonates on fracture healing have shown that these agents yield no clinically significant difference in healing times through endochondral fracture repair [55, 56]. Several studies have evaluated the effect of bisphosphonate therapy on osteoporotic women with distal radius fractures. Two such studies showed that postfracture bisphosphonate treatment led to increased BMD at the fracture site compared to placebo [57–59]. Two other studies evaluating the time to radiographic union reported no delay in healing with bisphosphonates versus control [60, 61]. Furthermore, analogous to animal studies, a meta-analysis of 14 randomized controlled trials has shown that bisphosphonates significantly reduce periprosthetic bone loss after total joint arthroplasty [62]. This effect is most pronounced in the first 3 months and more than 12 months after surgery. These two time points are thought to correspond to the two stages with the most active bone resorption: the first stage caused by the early iatrogenic damage of implant insertion during the surgery itself and the second due to late stress shielding and debris-induced osteolysis. Administration of zoledronic acid at least 2 weeks after surgical repair of a hip fracture has also been shown to increase hip BMD, as well as reduce clinical vertebral fractures, nonvertebral fractures, and all-cause mortality [63]. Interestingly, treatment before 2 weeks negates this reduction in mortality and fracture risk, although it does not affect time to fracture healing [1, 64–66]. This has prompted the treatment recommendation that bolus-dosed bisphosphonates be started between 2 and 12 weeks after a fragility fracture.

Denosumab

Overview

Denosumab is a fully recombinant monoclonal antibody that binds to receptor activator of nuclear factor κB ligand (RANKL), and is a potent antiresorptive treatment for osteoporosis. The antibody prevents osteoblast-produced RANKL

from reaching RANK receptors on the surface of osteoclasts and osteoclast precursors. This results in an inhibition of osteoclast recruitment, formation, activity, and survival, thereby decreasing bone resorption [67, 68]. In fact, while bisphosphonates primarily act by inhibiting mature osteoclast function, denosumab is able to virtually abolish osteoclastogenesis [69]. The antifracture efficacy of denosumab has been documented in the FREEDOM trial, which showed that denosumab reduced the risk of vertebral fracture by over 68 % [70, 71].

Animal studies

Similar to bisphosphonates, denosumab does not appear to impair healing in animal fracture models. Fractures healing by endochondral ossification in animals treated with denosumab also demonstrate increased callus volume and delayed remodeling. Unlike with bisphosphonates, which only increased callus tissue BMC, denosumab yielded increases in both BMC and BMD. The reason for this finding is unclear, and it may just be a chance phenomenon. Biomechanically, denosumab has been shown to increase torsional rigidity of the fractured bone. Interestingly, when healing mouse femurs underwent mechanical testing at 42 days postfracture, only 29 % of the denosumab-treated group had a refracture through the callus, compared to 57 % of alendronate-treated mice and 87 % of control mice. This suggests that despite its inhibitory effect on remodeling, denosumab does not impair bone formation or healing and may enhance the restoration of mechanical properties [69].

Clinical evidence

To date, there has been little published clinical data regarding fracture healing in denosumab-treated patients. The strongest evidence is provided by the FREEDOM trial, a large, multiinstitutional double-blind placebo-controlled study. In this study, 667 postmenopausal women were randomly assigned to denosumab or control, and fracture healing was evaluated in those who sustained a nonvertebral fracture during the study period. Denosumab did not delay fracture healing nor contribute to other complications, even when administered around the time of the fracture [68, 71]. These results suggest that denosumab therapy can be continued in the presence of a fracture without concern for impaired healing.

Calcitonin

Overview

Calcitonin is a calciotropic hormone that primarily inhibits bone resorption by decreasing the number and activity of osteoclasts [72]. Bone formation is also transiently increased, potentially due to osteoblast stimulation. Calcitonin has been shown to be beneficial in treating osteoporosis by stabilizing or increasing BMD and reducing the risk of vertebral fracture by 33 % [73]. Although it is a controversial observation not well studied in relation to recovery from fracture, calcitonin has been seen to exert an analgesic effect, possibly by elevating endorphin levels or inhibiting neuropeptide release [74].

Animal studies

Many animal studies have examined the effect of calcitonin on fracture healing. The majority of studies demonstrate enhanced callus formation with calcitonin treatment, although this finding may be attributed to publication bias as mixed results have been reported. These studies conclude that calcitonin stimulates early endochondral ossification, causing increased cartilage formation and earlier callus maturation. In addition, calcitonin enhances the biomechanical properties of the healing bone, such as fracture load and stiffness, which may contribute to earlier weight-bearing and mobilization [75, 76].

Clinical evidence

Few clinical studies have evaluated the role of calcitonin in human fractures. One randomized, double-blind, placebo-controlled study on calcitonin in elderly hip fracture patients showed no significant difference in mortality, length of hospital stay, or functional recovery between the two groups. However, after 3 months of treatment, X-rays showed a statistically significant difference in fracture fusion, with 84 % in the calcitonin group compared to 63 % in the placebo group [72]. In another double-blind, placebo-controlled trial, calcitonin led to reduced pain, earlier mobilization, and faster restoration of locomotor function in patients with osteoporotic vertebral crush fractures [74, 77]. The limited evidence suggests a potential benefit of calcitonin in fracture healing, but further studies are needed.

Estrogen and selective estrogen receptor modulators

Overview

The endogenous estrogen hormone, 17β-estradiol (estradiol), has a protective effect on bone. Its production decreases during menopause, which contributes to postmenopausal osteoporosis. Although estradiol supplementation has been useful in preventing postmenopausal osteoporotic bone loss, long-term estrogen replacement therapy (ERT) is associated with adverse effects including cardiovascular events and an increased risk of uterine and breast cancer [78–81]. This led to the development of SERMs, which provide the beneficial effects of estrogen on skeletal tissue without the negative effects

on reproductive tissue [82]. Raloxifene, the main SERM used in osteoporosis, exerts estrogenic effects on bone to decrease the rate of remodeling, attenuate osteoclast activity, and maintain osteoblastic activity [83]. In large treatment studies, raloxifene reduced the occurrence of vertebral fracture by 30–50 %, although it did not protect against hip fractures [84, 85].

Animal studies

In ovariectomized rats supplemented with either estrogen or raloxifene, both agents mildly suppressed callus remodeling but did not impede progression of fracture repair [86]. Although both drugs increased trabecular density and enhanced callus biomechanics, raloxifene increased total callus formation, while estrogen specifically increased endosteal bone formation [87]. In the same mouse model, estrogen and raloxifene yielded calluses with larger chondrocyte areas, greater mineralization, increased trabecular and neocortical thickness, and decreased time to fracture healing compared to controls [88, 89]. The treated calluses also had significantly increased force to failure and increased stiffness. Animal models thus demonstrate that estrogen and raloxifene not only increase chondrogenesis in the early phase of fracture healing but also enhance periosteal callus remodeling in later stages of the healing.

Clinical evidence

There has been little published clinical data regarding fracture healing in estrogen or raloxifene-treated patients.

Anabolic agents

Parathyroid hormone

Overview

PTH is a key regulator of calcium and phosphate metabolism. Clinically, it is used as an anabolic agent to treat severely osteoporotic patients at high risk for fragility fractures. Two different forms of the drug exist, PTH 1-34 and PTH 1-84. Both are approved for osteoporosis in Europe, while only PTH 1-34 (teriparatide) is approved in the USA. Teriparatide consists of the first 34 amino acids of PTH, which is considered the "active" part of the hormone, while PTH 1-84 also includes the remaining 50 amino acids, which is considered the "inactive" segment [90]. The two compounds are considered equivalent in terms of bone activity.

PTH exerts its anabolic effect by inhibiting the apoptosis of preosteoblasts, increasing their proliferation, and transforming bone lining cells into active osteoblasts, thus increasing osteoblast function and lifespan [91, 92]. This results in increased bone formation on all bone surfaces including endosteal bone, periosteal bone, and trabeculae [93]. It also increases trabecular connectivity and cortical bone thickness, which enhances the bone's microarchitecture and biomechanical properties. In fact, teriparatide can cause up to a 13 % increase in BMD at the lumbar spine after 2 years of therapy and reduce the risk of fracture by 65 and 53 % for vertebral and nonvertebral fractures, respectively [94].

Animal studies

Animal studies using supraphysiologic doses of PTH have demonstrated increased strength and callus quantity in the fracture site. Relative to controls, PTH-treated animals form a larger, denser, and more mature callus. The callus also mineralizes faster and has markedly improved biomechanical properties such as stiffness and torsional strength [95–99]. Teriparatide has even been shown to enhance the earliest stages of endochondral bone repair by increasing chondrocyte recruitment and rate of differentiation [100]. This suggests that PTH's effects extend beyond osteogenesis to influence chondrogenic proliferation and differentiation. Consequently, both cartilaginous and mineralized callus formations are increased during fracture healing [43, 101, 102]. The timing of PTH administration is important, with optimal healing observed with early treatment within 1 week of fracture [98, 103].

Clinical evidence

Although effective in treating osteoporosis, there are concerns that those doses (20–40 mcg total/dose) may not have the same effect on fracture healing as the supraphysiologic doses used in animal models (5–200 mcg/kg/dose) [43]. However, several clinical case reports, case series, and randomized, controlled studies have indicated that PTH may enhance bone healing, particularly in the distal radius, pelvis, and spine [104–111].

Two prospective randomized controlled studies investigated the role of PTH in fractures of the distal radius and pelvis. The first study evaluated teriparatide in postmenopausal women with distal radial fractures. Healing was assessed based on cortical bridging on plain radiographs, and significantly accelerated healing was noted in the 20-mcg dose group compared to controls (7.4 vs. 9.1 weeks). No effect was seen with the higher 40-mcg dose, which may have been due to the low sensitivity of using radiographic cortical bridging alone to detect healing of distal radius fractures [107]. Follow-up post hoc analysis evaluating callus robustness showed a dose-dependent improvement in early callus formation with PTH treatment [108].

A similar improvement was noted in the second study, which was conducted in Austria using PTH 1-84. This study

involved pelvic fractures of the ischial and pubic rami in elderly, osteoporotic women. Healing was also determined radiographically by the presence of cortical bridging, and the treatment group had shortened time to healing (7.8 vs. 12.6 weeks) and improved functional outcomes, as measured by a visual analog scale score for pain and a Timed "Up and Go" test [109]. However, the design of this study does result in some concern about the quality of the results. The lack of patient randomization, as every third patient was chronologically assigned to the treatment group, while the other two were assigned to the control group, is a limitation of the study. This resulted in unbalanced patient allocation and sample sizes of the treatment and control groups. In addition, the treatment patients were from a single institution, while the control patients were recruited from multiple institutions.

PTH's effect on bone healing has also been demonstrated in spine fusion studies. These studies evaluated fusion rate and pedicle screw loosening in osteoporotic women undergoing instrumented posterolateral lumbar fusion. Patients were started on either bisphosphonate or teriparatide 2 months prior to surgery and continued treatment for 8 months postoperatively. Based on periodic follow-up radiographs, accelerated fusion was noted with teriparatide compared to bisphosphonate, and compared to both bisphosphonates and unmedicated controls, the teriparatide group had decreased screw loosening and increased bone mass [110, 111].

More recently, several studies have evaluated the use of teriparatide in complications from long-term bisphosphonate bone suppression. Histological analysis of bisphosphonate-associated incomplete atypical femoral fractures has shown that there are no signs of callus formation or remodeling within the fracture gap itself, in spite of the fact that the bone adjacent to the fracture site has remodeling activity. This has been explained by the fact that in these patients, normal gait produces strains in the fracture gap that are too large for cell survival. Without fracture surface resorption, remodeling units cannot bridge the fracture gap and healing cannot occur [112]. In this patient population, PTH treatment resulted in a significant improvement in remodeling intensity, as evidenced by elevations of bone turnover markers, increased deposition of newly formed less mineralized bone, and increased removal of older densely mineralized bone [113]. In a retrospective cohort study examining patients surgically treated for both complete and incomplete atypical femoral fractures, time to fracture healing and frequency of delayed healing or nonunion were significantly reduced in the group treated with teriparatide compared to the group that was not [114]. Smaller studies have also demonstrated a potential role for teriparatide in reversing bisphosphonate-related osteonecrosis of the jaw, further suggesting that PTH may enhance bone activity and counteract bone remodeling suppression associated with prolonged bisphosphonate use [115]. These findings add to the existing body of clinical data supporting the use of PTH in fracture healing.

Strontium ranelate

Overview

SR is a unique antiresorptive drug that may have anabolic properties. As an antiresorptive agent, it targets osteoclasts to inhibit their differentiation and promote their apoptosis. The anabolic effects are more controversial but are thought to be via enhanced proliferation, differentiation, and activation of preosteoblasts [116]. Consisting of two strontium atoms coupled to ranelic acid, SR incorporates into bone and replaces some calcium with strontium, which leads to an increase in BMD [90]. It also improves bone quality by increasing mineral apposition rate, improving trabecular microarchitecture, and enhancing cortical thickness [117]. The increased robustness is supported by clinical trials of SR therapy in osteoporotic women, which show increased lumbar spine BMD by 14.4 % and reduced vertebral and nonvertebral fractures by 41 and 16 %, respectively [118, 119]. Although approved in Europe by the European Medicines Agency (EMA), SR was never submitted to the Food and Drug Administration (FDA) for approval to treat postmenopausal osteoporosis in the USA.

Animal studies

Animal models have shown SR incorporates into newly formed callus tissue, but the effect on fracture healing is dependent on bone quality. In rat studies, SR had no effect on fractures in normal bone but improved healing in osteoporotic bone [120]. In ovariectomized rats, SR significantly increased callus bone formation, maturity, and mineralization, resulting in greater callus volume and BMD. The microstructural properties of the callus were also enhanced via increased trabecular quantity and density, translating to greater mechanical strength and fracture stiffness [121, 122].

Clinical evidence

At this time, there is little published data regarding fracture healing in SR-treated patients. Two small case series of two and four patients with delayed union or nonunion of long bone fractures reported radiographic signs of healing and clinical improvement following SR therapy [123, 124]. Yet due to the low level of evidence, more rigorous studies are required to evaluate SR's effect on fracture healing in humans.

Conclusion

Understanding how various osteoporosis medications influence fracture healing is critical in the management of osteoporotic patients. This review summarizes the currently published literature on how these medications influence the fracture healing process. The review is limited by the study designs of the included articles as well as publication bias. It is possible that there are a significant number of unpublished, withdrawn, or uncompleted studies that have been performed which had negative results. In fact, a search of both the National Institutes of Health and European Union clinical trial registries shows that there are currently 14 listed clinical trials evaluating osteoporotic medications in fracture healing, 8 of which are active, 3 of which have been completed, and 3 of which were prematurely terminated [125, 126]. Of the 6 clinical trials listed as completed or prematurely terminated, 2 have presented published data, both concerning PTH's role in fracture healing. In addition, many of the clinical studies in this review evaluated shaft fracture healing by endochondral ossification and external callus formation, which may involve different mechanisms of healing than more commonly seen metaphyseal fractures. Nonetheless, considerable work has been done with animal models characterizing the behavior of these medications on the fracture healing process. These studies have shown that neither antiresorptive nor anabolic medications interfere with fracture healing and may even lead to more robust mechanical properties. Although clinical studies are limited, early research has demonstrated positive effects, particularly with PTH. Further clinical trials are required to determine the optimal use of these systemic agents to enhance bone repair and decrease future fracture risk.

Compliance with ethical standards

Conflicts of interest None.

References

1. Rebolledo BJ, Unnanuntana A, Lane JM (2011) A comprehensive approach to fragility fractures. J Orthop Trauma 25(9):566–573
2. Goldhahn J, Little D, Mitchell P et al (2010) Evidence for anti-osteoporosis therapy in acute fracture situations—recommendations of a multidisciplinary workshop of the International Society for Fracture Repair. Bone 46(2):267–271
3. Namkung-Matthai H, Appleyard R, Jansen J et al (2001) Osteoporosis influences the early period of fracture healing in a ratosteoporotic model. Bone 28:80–86
4. Wang JW, Li W, Xu SW et al (2005) Osteoporosis influences the middle and late periods of fracture healing in a rat osteoporotic model. Chin J Traumatol 8:111–116
5. McClung MR, Grauer A, Boonen S et al (2014) Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 370(5):412–420
6. Nakamura T, Shiraki M, Fukunaga M et al (2014) Effect of the cathepsin K inhibitor odanacatib administered once weekly on bone mineral density in Japanese patients with osteoporosis—a double-blind, randomized, dose-finding study. Osteoporos Int 25:367–376
7. Soung DY, Gentile MA, Duong LT, Drissi H (2013) Effects of pharmacological inhibition of cathepsin K on fracture repair in mice. Bone 55(1):248–255
8. Virk MS, Alaee F, Tang H et al (2013) Systemic administration of sclerostin antibody enhances bone repair in a critical-sized femoral defect in a rat model. J Bone Joint Surg Am 95(8):694–701
9. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY et al (2004) Effect of vitamin D on falls: a meta-analysis. JAMA 291(16):1999–2006
10. Gorter EA, Hamdy NA, Appelman-Dijkstra NM, Schipper IB (2014) The role of vitamin D in human fracture healing: a systemic review of the literature. Bone 64C:288–297
11. Delgado-Martinez AD, Martinez ME, Carrascal MT, Rodriguez-Avial M, Munuera L (1998) Effect of 25-OH-vitamin D on fracture healing in elderly rats. J Orthop Res 16(6):650–653
12. Omeroglu H, Ates Y, Akkus O, Korkusuz F, Bicimoglu A, Akkas N (1997) Biomechanical analysis of the effects of single high-dose vitamin D3 on fracture healing in a healthy rabbit model. Arch Orthop Trauma Surg 116(5):271–274
13. Lindgren JU, Narechania RG, McBeath AA, Lange TA, DeLuca HF (1981) Effects of 1,24 dihydroxyvitamin D3 and calcitonin on fracture healing in adult rats. Clin Orthop Relat Res 160:304–308
14. Brumbaugh PF, Speer DP, Pitt MJ (1982) 1 Alpha, 25-dihydroxyvitamin D3 a metabolite of vitamin D that promotes bone repair. Am J Pathol 106(2):171–179
15. Kubo T, Shiga T, Hashimoto J, Yoshioka M, Honjo H, Urabe M et al (1999) Osteoporosis influences the late period of fracture healing in a rat model prepared by ovariectomy and low calcium diet. J Steroid Biochem Mol Biol 68(5–6):197–202
16. Jingushi S, Iwaki A, Higuchi O, Azuma Y, Ohta T, Shida JI et al (1998) Serum 1alpha,25-dihydroxyvitamin D3 accumulates into the fracture callus during rat femoral fracture healing. Endocrinology 139(4):1467–1473
17. Seo EG, Einhorn TA, Norman AW (1997) 24R,25-Dihydroxyvitamin D3: an essential vitamin D3 metabolite for both normal bone integrity and healing of tibial fracture in chicks. Endocrinology 138(9):3864–3872
18. Kato A, Seo EG, Einhorn TA, Bishop JE, Norman AW (1998) Studies on 24R,25-dihydroxyvitamin D3: evidence for a nonnuclear membrane receptor in the chick tibial fracture-healing callus. Bone 23(2):141–146
19. Pedrozo HA, Schwartz Z, Rimes S et al (1999) Physiological importance of the 1,25(OH)2D3 membrane receptor and evidence for a membrane receptor specific for 24,25(OH)2D3. J Bone Miner Res 14(6):856–867
20. Saito M, Shiraishi A, Ito M, Sakai S, Hayakawa N, Mihara M et al (2010) Comparison of effects of alfacalcidol and alendronate on mechanical properties and bone collagen cross-links of callus in the fracture repair rat model. Bone 46(4):1170–1179
21. van Leeuwen JP, van Driel M, van den Bemd GJ, Pols HA (2001) Vitamin D control of osteoblast function and bone extracellular matrix mineralization. Crit Rev Eukaryot Gene Expr 11:199–226
22. Anderson PH, Atkins GJ (2008) The skeleton as an intracrine organ for vitamin D metabolism. Mol Asp Med 29:397–406
23. van Driel M, Koedam M, Buurman CJ, Hewison M, Chiba H, Uitterlinden AG et al (2006) Evidence for auto/paracrine actions of vitamin D in bone: 1alpha-hydroxylase expression and activity in human bone cells. FASEB J 20:2417–2419
24. van Driel M, Koedam M, Buurman CJ, Roelse M, Weyts F, Chiba H et al (2006) Evidence that both 1 alpha,25-dihydroxyvitamin D-

3 and 24-hydroxylated D-3 enhance human osteoblast differentiation and mineralization. J Cell Biochem 99:922–935
25. Fu L, Tang T, Miao Y, Hao Y, Dai K (2009) Effect of 1,25-dihydroxy vitamin D3 on fracture healing and bone remodeling in ovariectomized rat femora. Bone 44(5):893–898
26. Kogawa M, Anderson PH, Findlay DM, Morris HA, Atkins GJ (2010) The metabolism of 25(OH)vitamin D3 by osteoclasts and their precursors regulates the differentiation of osteoclasts. J Steroid Biochem Mol Biol 121:277–280
27. Mee AP, Hoyland JA, Braidman IP, Freemont AJ, Davies M, Mawer EB (1996) Demonstration of vitamin D receptor transcripts in actively resorbing osteoclasts in bone sections. Bone 18:295–299
28. Qi DY, Perkins SL, Kling SJ, Russell RG (1999) Divergent regulation of 1,25-dihydroxyvitamin D3 on human bone marrow osteoclastogenesis and myelopoiesis. J Cell Biochem 72:387–395
29. Thavarajah M, Evans DB, Kanis JA (1991) 1,25(OH)2D3 induces differentiation of osteoclast-like cells from human bone marrow cultures. Biochem Biophys Res Commun 176:1189–1195
30. Doetsch AM, Faber J, Lynnerup N, Watjen I, Bliddal H, Danneskiold-Samsoe B (2004) The effect of calcium and vitamin D3 supplementation on the healing of the proximal humerus fracture: a randomized placebo-controlled study. Calcif Tissue Int 75(3):183–188
31. Brinker MR, O'Connor DP, Monla YT, Earthman TP (2007) Metabolic and endocrine abnormalities in patients with nonunion. J Orthop Trauma 21(8):557–570
32. Bolland MJ, Barber PA, Doughty RN et al (2008) Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 336:262
33. Bolland MJ, Avenell A, Baron JA et al (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341:c3691
34. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G (2005) Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 294(19):2336–2341
35. Sakuma M, Endo N, Oinuma T et al (2006) Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int 17:1608–1614
36. Russell RG (2011) Bisphosphonates: the first 40 years. Bone 49: 2–19
37. Chapurlat RD, Palermo L, Ramsay P, Cummings SR (2005) Risk of fracture among women who lose bone density during treatment with alendronate. The fracture intervention. Osteoporos Int 16(7): 842–848
38. McDonald MM, Dulai S, Godfrey C, Amanat N, Sztynda T, Little DG (2008) Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling. Bone 43(4):653–662
39. Matos MA, Tannuri U, Guarniero R (2010) The effect of zoledronate during bone healing. J Orthop Traumatol 11(1):7–12
40. Amanat N, McDonald M, Godfrey C, Bilston L, Little D (2007) Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. J Bone Miner Res 22(6):867–876
41. Li C, Mori S, Li J, Kaji Y, Akiyama T, Kawanishi J et al (2001) Long-term effect of incadronate disodium (YM-175) on fracture healing of femoral shaft in growing rats. J Bone Miner Res 16(3): 429–436
42. Fleisch H (2001) Can bisphosphonates be given to patients with fractures? J Bone Miner Res 16(3):437–440
43. Kurth AH, Eberhardt C, Muller S, Steinacker M, Schwarz M, Bauss F (2005) The bisphosphonate ibandronate improves implant integration in osteopenic ovariectomized rats. Bone 37: 204–210
44. Chen B, Li Y, Yang X, Xu H, Xie D (2013) Zoledronic acid enhances bone-implant osseointegration more than alendronate and strontium ranelate in ovariectomized rats. Osteoporos Int 24: 2115–2121
45. Skripitz R, Johansson HR, Ulrich SD, Werner A, Aspenberg P (2009) Effect of alendronate and intermittent parathyroid hormone on implant fixation in ovariectomized rats. J Orthop Sci 14:138–143
46. Chen BL, Xie DH, Zheng ZM, Lu W, Ning CY, Li YQ et al (2011) Comparison of the effects of alendronate sodium and calcitonin on bone-prosthesis osseointegration in osteoporotic rats. Osteoporos Int 22:265–270
47. Viera-Negron YE, Ruan WH, Winger JN, Hou X, Sharawy MM, Borke JL (2008) Effect of ovariectomy and alendronate on implant osseointegration in rat maxillary bone. J Oral Implantol 34: 76–82
48. Qi M, Hu J, Li J, Li J, Dong W, Feng X et al (2012) Effect of zoledronate acid treatment on osseointegration and fixation of implants in autologous iliac bone grafts in ovariectomized rabbits. Bone 50:119–127
49. Tsetsenekou E, Papadopoulos T, Kalyvas D, Papaioannou N, Tangl S, Watzek G (2012) The influence of alendronate on osseointegration of nanotreated dental implants in New Zealand rabbits. Clin Oral Implants Res 23:659–666
50. Yildiz A, Esen E, Kurkcu M, Damlar I, Daglioglu K, Akova T (2010) Effect of zoledronic acid on osseointegration of titanium implants: an experimental study in an ovariectomized rabbit model. J Oral Maxillofac Surg 68:515–523
51. Gao Y, Zou S, Liu X, Bao C, Hu J (2009) The effect of surface immobilized bisphosphonates on the fixation of hydroxyapatite-coated titanium implants in ovariectomized rats. Biomaterials 30: 1790–1796
52. Peter B, Gauthier O, Laib S, Bujoli B, Guicheux J, Janvier P et al (2006) Local delivery of bisphosphonate from coated orthopedic implants increases implants mechanical stability in osteoporotic rats. J Biomed Mater Res A 76:133–143
53. Stadelmann VA, Gauthier O, Terrier A, Bouler JM, Pioletti DP (2008) Implants delivering bisphosphonate locally increase periprosthetic bone density in an osteoporotic sheep model. A pilot study. Eur Cell Mater 16:10–16
54. Bukata SV (2011) Systemic administration of pharmacological agents and bone repair: what can we expect. Injury 42(6):605–608
55. Rozental TD, Vazquez MA, Chacko AT, Ayogu N, Bouxsein ML (2009) Comparison of radiographic fracture healing in the distal radius for patients on and off bisphosphonate therapy. J Hand Surg Am 34(4):595–602
56. Colon-Emeric C, Nordsletten L, Olson S, Major N, Boonen S, Haentjens P et al (2011) Association between timing of zoledronic acid infusion and hip fracture healing. Osteoporos Int 22(8):2329–2336
57. Adolphson P, Abbaszadegan H, Boden H, Salemyr M, Henriques T (2000) Clodronate increases mineralization of callus after Colles' fracture: a randomized, double-blind, placebo-controlled, prospective trial in 32 patients. Acta Orthop Scand 71(2):195–200
58. van der Poest Clement E, Patka P, Vandormael K, Haarman H, Lips P (2000) The effect of alendronate on bone mass after distal forearm fracture. J Bone Miner Res 15(3):586–593
59. Koester MC, Spindler KP (2006) Pharmacologic agents in fracture healing. Clin Sports Med 25(1):63–73
60. Gong HS, Song CH, Lee YH, Rhee SH, Lee HJ, Baek GH (2012) Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures. J Bone Joint Surg Am 94:1729–1736
61. Uchiyama S, Itsubo T, Nakamura K et al (2013) Effect of early administration of alendronate after surgery for distal radial

fragility fracture on radiological fracture healing time. Bone Joint J 95-B(11):1544–1550
62. Lin T, Yan S-G, Cai X-Z, Ying Z-M (2012) Bisphosphonates for periprosthetic bone loss after joint arthroplasty: a meta-analysis of 14 randomized controlled trials. Osteoporos Int 23:1823–1834
63. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C et al (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357(18):1799–1809
64. Eriksen EF, Lyles KW, Colon-Emeric CS, Pieper CF, Magaziner JS, Adachi JD et al (2009) Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. J Bone Miner Res 24(7):1308–1313
65. Kim TY, Ha YC, Kang BJ, Lee YK, Koo KH (2012) Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures? J Bone Joint Surg (Br) 94-B:956–960
66. McClung M, Harris ST, Miller PD et al (2013) Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 126(1):13–20
67. Lewiecki EM (2010) Treatment of osteoporosis with denosumab. Maturitas 66(2):182–186
68. Moen MD, Keam SJ (2011) Denosumab: a review of its use in the treatment of postmenopausal osteoporosis. Drugs Aging 28(1): 63–82
69. Gerstenfeld LC, Sacks DJ, Pelis M, Mason ZD, Graves DT, Barrero M et al (2009) Comparison of effects of the bisphosphonate alendronate versus the RANKL inhibitor denosumab on murine fracture healing. J Bone Miner Res 24(2):196–208
70. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR et al (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361(8):756–765
71. Adami S, Libanati C, Boonen S, Cummings SR, Ho PR, Wang A, Siris E, Lane JM et al (2012) Denosumab treatment in postmenopausal women with osteoporosis does not interfere with fracture-healing: results from the FREEDOM trial. J Bone Joint Surg Am 94:2113–2119
72. Huusko TM, Karppi P, Kautiainen H, Suominen H, Avikainen V, Sulkava R (2002) Randomized, double-blind, clinically controlled trial of intranasal calcitonin treatment in patients with hip fracture. Calcif Tissue Int 71(6):478–484
73. Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S et al (2000) A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 109(4):267–276
74. Lyritis G, Boscainos PJ (2001) Calcitonin effects on cartilage and fracture healing. J Musculoskelet Neuronal Interact 2(2):137–142
75. Bulbul M, Esenyel CZ, Esenyel M, Ayanoglu S, Bilgic B, Gulmez T (2008) Effects of calcitonin on the biomechanics, histopathology, and radiography of callus formation in rats. J Orthop Sci 13(2): 136–144
76. Lyritis GP, Tsakalakos N, Magiasis B, Karachalios T, Yiatzides A, Tsekoura M (1991) Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures: a double-blind placebo-controlled clinical study. Calcif Tissue Int 49(6):369–372
77. Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG (1997) Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. Acta Orthop Scand Suppl 275:112–114
78. Migliaccio S, Brama M, Spera G (2007) The differential effects of bisphosphonates, SERMS (selective estrogen receptor modulators), and parathyroid hormone on bone remodeling in osteoporosis. Clin Interv Aging 2(1):55–64
79. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K et al (2002) Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 287(7):847–857
80. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ et al (1995) The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 332(24):1589–1593
81. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288(3):321–333
82. Sahiner T, Aktan E, Kaleli B, Oguzhanoglu A (1998) The effects of postmenopausal hormone replacement therapy on sympathetic skin response. Maturitas 30(1):85–88
83. Taranta A, Brama M, Teti A, De luca V, Scandurra R, Spera G et al (2002) The selective estrogen receptor modulator raloxifene regulates osteoclast and osteoblast activity in vitro. Bone 30(2):368–376
84. Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT et al (2008) Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Miner Res 23(1):112–120
85. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282(7): 637–645
86. Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M et al (2002) Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res 17(12):2237–2246
87. Stuermer EK, Sehmisch S, Rack T, Wenda E, Seidlova-Wuttke D, Tezval M et al (2010) Estrogen and raloxifene improve metaphyseal fracture healing in the early phase of osteoporosis. A new fracture-healing model at the tibia in rat. Langenbeck's Arch Surg 395(2):163–172
88. Beil FT, Barvencik F, Gebauer M, Seitz S, Rueger JM, Ignatius A et al (2010) Effects of estrogen on fracture healing in mice. J Trauma 69(5):1259–1265
89. Spiro AS, Khadem S, Jeschke A, Marshall RP, Pogoda P, Ignatius A, Amling M, Beil FT (2013) The SERM raloxifene improves diaphyseal fracture healing in mice. J Bone Miner Metab 31: 629–636
90. Sibai T, Morgan EF, Einhorn TA (2011) Anabolic agents and bone quality. Clin Orthop Relat Res 469(8):2215–2224
91. Dobnig H, Turner RT (1995) Evidence that intermittent treatment with parathyroid hormone increases bone formation in adult rats by activation of bone lining cells. Endocrinology 136(8):3632–3638
92. Manolagas SC (2000) Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 21(2):115–137
93. Friedl G, Turner RT, Evans GL, Dobnig H (2007) Intermittent parathyroid hormone (PTH) treatment and age-dependent effects on rat cancellous bone and mineral metabolism. J Orthop Res 25(11):1454–1464
94. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY et al (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344(19):1434–1441
95. Andreassen TT, Ejersted C, Oxlund H (1999) Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 14(6):960–968

96. Andreassen TT, Willick GE, Morley P, Whitfield JF (2004) Treatment with parathyroid hormone hPTH(1-34), hPTH(1-31), and monocyclic hPTH(1-31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. Calcif Tissue Int 74(4):351–356
97. Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH et al (2005) Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Joint Surg Am 87(4):731–741
98. Manabe T, Mori S, Mashiba T, Kaji Y, Iwata K, Komatsubara S et al (2007) Human parathyroid hormone (1-34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. Bone 40(6):1475–1482
99. Komatsubara S, Mori S, Mashiba T, Nonaka K, Seki A, Akiyama T et al (2005) Human parathyroid hormone (1-34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. Bone 36(4):678–687
100. Kakar S, Einhorn TA, Vora S, Miara LJ, Hon G, Wigner NA et al (2007) Enhanced chondrogenesis and Wnt signaling in PTH-treated fractures. J Bone Miner Res 22(12):1903–1912
101. Nakajima A, Shimoji N, Shiomi K, Shimizu S, Moriya H, Einhorn TA et al (2002) Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1-34). J Bone Miner Res 17(11):2038–2047
102. Nakazawa T, Nakajima A, Shiomi K, Moriya H, Einhorn TA, Yamazaki M (2005) Effects of low-dose, intermittent treatment with recombinant human parathyroid hormone (1-34) on chondrogenesis in a model of experimental fracture healing. Bone 37(5):711–719
103. Jorgensen NR, Schwarz P (2011) Effects of anti-osteoporosis medications on fracture healing. Curr Osteoporos Rep 9(3):149–155
104. Reynolds DG, Shaikh S, Papuga MO, Lerner AL, O'Keefe RJ, Schwarz EM et al (2009) muCT-based measurement of cortical bone graft-to-host union. J Bone Miner Res 24(5):899–907
105. Rubery PT, Bukata SV (2010) Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. J Spinal Disord Tech 23(2):151–155
106. Bukata SV, Puzas JE (2010) Orthopedic uses of teriparatide. Curr Osteoporos Rep 8(1):28–33
107. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K et al (2010) Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 25(2):404–414
108. Aspenberg P, Johansson T (2010) Teriparatide improves early callus formation in distal radial fractures. Acta Orthop 81(2):234–236
109. Peichl P, Holzer LA, Maier R, Holzer G (2011) Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 93(17):1583–1587
110. Ohtori S, Inoue G, Orita S et al (2012) Teriparatide accelerates lumbar posterolateral fusion in women with postmenopausal osteoporosis. Spine 37(23):E1464–E1468
111. Ohtori S, Inoue G, Orita S et al (2013) Comparison of teriparatide and bisphosphonate treatment to reduce pedicle screw loosening after lumbar spinal fusion surgery in postmenopausal women with osteoporosis from a bone quality perspective. Spine 38(8):E487–E492
112. Schilcher J, Sandberg O, Isaksson H, Aspenberg P (2014) Histology of 8 atypical femoral fractures: remodeling but no healing. Acta Orthop 85(3):280–286
113. Chiang CY, Zebaze RM, Ghasem-Zadeh A et al (2013) Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. Bone 52(1):360–365
114. Miyakoshi N, Aizawa T, Shimada Y et al (2015) Healing of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: a comparison between treatment with and without teriparatide. J Bone Miner Metab 33:553–559
115. Kim KM, Park W, Oh SY et al (2014) Distinctive role of 6-month teriparatide treatment on intractable bisphosphonate-related osteonecrosis of the jaw. Osteoporos Int 25(5):1625–1632
116. Habermann B, Kafchitsas K, Olender G, Augat P, Kurth A (2010) Strontium ranelate enhances callus strength more than PTH 1-34 in an osteoporotic rat model of fracture healing. Calcif Tissue Int 86(1):82–89
117. Arlot ME, Jiang Y, Genant HK, Zhao J, Burt-Pichat B, Roux JP et al (2008) Histomorphometric and microCT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. J Bone Miner Res 23(2):215–222
118. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD et al (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350(5):459–468
119. Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML et al (2008) Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum 58(6):1687–1695
120. Cebesoy O, Tutar E, Kose KC, Baltaci Y, Bagci C (2007) Effect of strontium ranelate on fracture healing in rat tibia. Joint Bone Spine 74(6):590–593
121. Li YF, Luo E, Feng G, Zhu SS, Li JH, Hu J (2010) Systemic treatment with strontium ranelate promotes tibial fracture healing in ovariectomized rats. Osteoporos Int 21(11):1889–1897
122. Ozturan KE, Demir B, Yucel I, Cakici H, Yilmaz F, Haberal A (2011) Effect of strontium ranelate on fracture healing in the osteoporotic rats. J Orthop Res 29(1):138–142
123. Alegre DN, Ribeiro C, Sousa C, Correia J, Silva L, de Almeida L (2012) Possible benefits of strontium ranelate in complicated long bone fractures. Rheumatol Int 32(2):439–443
124. Tarantino U, Celi M, Saturnino L, Scialdoni A, Cerocchi I (2010) Strontium ranelate and bone healing: report of two cases. Clin Case Miner Bone Metab 7(1):65–68
125. ClinicalTrials.gov. National Institutes of Health (2015) Web https://clinicaltrials.gov/ct2/home
126. EU Clinical Trials Register. European Medicines Agency (2015) Web. https://www.clinicaltrialsregister.eu/ctr-search/search