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An ESCEO Consensus Paper

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Implications for Fracture Healing of Current and New Osteoporosis Treatments: An ESCEO Consensus Paper

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Abstract Osteoporotic fracture healing is critical to clinical outcome in terms of functional recovery, morbidity, and quality of life. Osteoporosis treatments may affect bone repair, so insights into their impact on fracture healing are important. We reviewed the current evidence for an impact of osteoporosis treatments on bone repair. Treatment with bisphosphonate in experimental models is

associated with increased callus size and mineralization, reduced callus remodeling, and improved mechanical strength. Local and systemic bisphosphonate treatment may improve implant fixation. No negative impact on fracture healing has been observed, even after major surgery or when administered immediately after fracture. Experimental data for denosumab and raloxifene suggest

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no negative implications for bone repair. The extensive experimental results for teriparatide indicate increased callus formation, improved biomechanical strength, and greater external callus volume and total bone mineral content and density. Case reports and a randomized trial have produced mixed results but are consistent with a positive impact of teriparatide on clinical fracture healing. Studies with strontium ranelate in models of fracture healing indicate that it is associated with improved bone microstructure, callus volume, and biomechanical properties. Finally, there is experimental evidence for a beneficial effect of some of the agents currently being developed for osteoporosis, notably sclerostin antibody and DKK1 antibody. There is currently no evidence that osteoporosis treatments are detrimental for bone repair and some promising experimental evidence for positive effects on healing, notably for agents with a bone-forming mode of action, which may translate into therapeutic applications.

Keywords Fractures · Healing · Bone formation · Osteoporosis · Treatment

The ultimate consequence of osteoporosis is fragility fracture. The subsequent regeneration of bone occurs in three stages, with inflammatory, reparative, and remodeling phases. The initial trauma provokes an inflammatory response, involving the release of a variety of substances including fibronectin, growth factors, fibroblasts, endothelial cells, and osteoblasts, which act to fill the fracture gap with granulosomatous tissue. The reparative phase involves a periosteal response with angiogenesis and formation of connective tissue and soft callus, which is gradually replaced by immature woven bone via intramembranous or endochondral bone formation. In the final remodeling phase, the woven bone callus is gradually replaced by lamellar bone.

Patients with osteoporosis are significantly more likely to suffer a fracture than the general population, and

management of these fractures remains a major challenge in orthopedics [1]. Whether osteoporotic bone has an increased healing time and a higher risk of non-union is still under debate; however, osteoporotic bone does have an impaired ability to hold screws due to cortical thinning, rarefied trabecular structure, and the presence of voids due to the crushing of cancellous bone after fracture reduction [2]. This complicates surgery, and failure rates of fracture fixation in osteoporotic bone range from 10% to 25% [3]. Any pharmacological intervention that improves bone repair, fracture healing, and implant fixation (i.e., osseointegration) would therefore constitute a considerable advance in reducing osteoporosis-associated morbidity. Indeed, while the main goal of osteoporosis treatment is to prevent fracture, it should also ideally have a positive, or at least neutral, effect on bone repair.

Many drugs affect the processes of bone repair [4]. Some have a negative effect, such as glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs), which act on the vascular supply during the inflammatory phase. The delay in fracture healing under NSAIDs is mostly based on numerous animal experiments and retrospective studies in humans, but randomized controlled trials (RCTs) have failed to confirm this effect up to now [5]. A number of drugs have been surmised to have positive effects, such as growth factors and prostaglandins; but there is currently no evidence supporting their clinical application. Osteoporosis drugs would be expected to affect the remodeling phase of bone repair but not the inflammatory and reparative phases. This is an important field of research since patients with osteoporosis are likely to be receiving an osteoporosis drug at the time of fracture or to be prescribed one shortly after the event.

The issue of bone repair has been the subject of two previous reports from the Group for the Respect of Ethics and Excellence in Science (GREES) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) [6, 7]. The first paper identified critical issues for clinical trials in fracture healing [6] and called for guidelines for trials designed to demonstrate positive or negative impacts of agents on fracture healing. A systematic review of the reporting of complications in orthopedic trials subsequently highlighted the necessity of such guidelines [8], and two multicenter open cohort studies have been set up to measure prospectively complication rates in osteoporosis [9].

The multitude of parameters involved makes any impact on bone repair difficult to measure and study. There is a considerable amount of data from experimental animal models of bone repair but little clinical trial evidence. The second report therefore defined themes for primary study end points in clinical trials [7]: acceleration of fracture union combined with faster return to normal function and

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reduction of complication rates. One of the main challenges in RCTs is the standardization of orthopedic interventions, which can be highly variable since no two surgeons act in the same way or with the same level of surgical expertise [10].

The ESCEO and GREES articles have identified a number of avenues for research [6, 7], including further exploration of how osteoporosis treatments act on bone repair, which is proving to be a complex issue and a rapidly evolving field [11]. This article is the result of a recent meeting of an ESCEO working group, which reviewed the current evidence for an impact of osteoporosis treatments on bone repair.

Methods

Relevant articles, reviews, and case reports were identified through a PubMed/MEDLINE search of English-language articles published between 1990 and March 2011. The search strategy included the terms “osteoporosis,” “osteoporosis treatment,” “bisphosphonate” (“alendronate,” “risedronate,” “zoledronic acid,” “ibandronate,” “pamidronate,” and “icandronate”), “denosumab,” “SERMs” (“raloxifene,” “bazodoxifene,” and “lasofoxifene”), “strontium ranelate,” “teriparatide,” “PTH,” “sclerostin antibody,” “DKK1 antibody,” “bone morphogenetic protein,” “fracture healing,” “fracture union,” “bone repair,” “osseous regeneration,” “osseous wound healing,” and “osseointegration.” Separate sub-searches were also performed using a cross-search of the above terms combined as well as the reference lists of the selected articles. Overall, 330 articles were detected, 71 of which were selected by the authors for inclusion in this review.

Bisphosphonates

There has been some debate regarding the impact of bisphosphonates on fracture union and bone repair [12, 13]. The concerns are primarily linked to the mode of action of bisphosphonates, which prevent osteoporotic fracture by suppression of bone resorption. This might be expected to have an impact on the third phase of bone repair, i.e., the remodeling phase [14]. Moreover, oral and intravenous bisphosphonates are known to be preferentially deposited at the site of acute fracture [15], which may exacerbate any action they have on bone repair. The debate has been fueled by recent case reports of atypical subtrochanteric fractures in patients receiving long-term treatment with bisphosphonates [16–18].

Experimental Evidence

The experimental evidence for the effects of bisphosphonates in animal models of bone repair and fracture is, on the whole, positive. There have been studies using a variety of bisphosphonates, including alendronate [14, 19], risedronate [20], zoledronic acid [15], pamidronate [21], and incadronate [22, 23]. Net osteoblast function does not appear to be impaired [19]. Most studies suggest that treatment with bisphosphonate is associated with an increase in callus size and mineralization [15, 21–23] or a neutral effect [12, 19]. There is no experimental evidence for a negative effect on callus formation [12]. In fact, bisphosphonates were often accompanied by an increase in callus mechanical strength compared with control animals [15, 19, 21]. According to some results, treatment with bisphosphonate slows callus remodeling and the removal of cartilage, which may delay the completion of the fracture-healing process [14, 19]. On the other hand, other results suggest that bisphosphonates do not affect long bone-fracture healing in the long term [23], though they may delay the remodeling process in the immediate postfracture period. A study with zoledronic acid found that the timing of administration was important and that delaying administration by 2 weeks produced larger and stronger callus [15]. It appears that delayed injection increased uptake efficacy of the agent in the callus.

The effect of bisphosphonates on osseointegration and implant fixation has been investigated in a variety of animal experiments [13]. In one study involving implantation of pamidronate-coated screws into the tibia of Sprague–Dawley rats, local application of bisphosphonate was found to improve pull-out force by 28% after 2 weeks ($p = 0.0009$ vs. control) and pull-out energy by 90% [24]. These results were confirmed in a similar rat model with ibandronate, in which either local or systemic application of the bisphosphonate improved screw fixation [25].

Clinical Evidence

Data from a double-blind RCT on the impact of bisphosphonate treatment on fracture healing, from the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) Recurrent Fracture trial in patients after hip fracture [26], which included blinded and centralized adjudication of hip radiographs and clinical files, have recently become available. Delayed fracture healing was defined according to clinical criteria (persistent pain or inability to bear weight) and radiographic criteria at least 6 weeks after surgical repair (persistence of fracture line, appearance of new fracture line, displacement of fracture, or lack of callus formation or fracture consolidation) [26]. The results indicated no significant difference in

delayed hip fracture healing defined according to these criteria with zoledronic acid (34 cases [3.2%] vs. 29 cases [2.7%] on placebo, $p = 0.61$). This applied even when the drug was infused in the immediate postoperative period, and multivariable logistic regression confirmed that there was no association between timing of administration and risk for delayed fracture repair with use of zoledronic acid (odds ratio [OR] = 1.21, 95% confidence interval [CI] 0.74–1.99, $p = 0.44$) [27]. While these data are reassuring with respect to the use of bisphosphonates in patients after fracture, they should be treated with some caution. For example, the HORIZON population had one-third of the mortality of a typical hip-fracture population and, therefore, constituted a relatively “healthy” subset of the hip-fracture population. Nevertheless, particular strengths of the study included its prospective design and double-blind character, with well-defined and well-assessed end points as well as independent and blinded adjudication.

Two small placebo-controlled studies indicated that 1-year treatment with alendronate could prevent bone loss after fracture and did not affect fracture healing [28, 29]. On the other hand, data from small studies and retrospective case–control studies with bisphosphonates have been less consistent but should be considered with caution due to potential confounding by unmeasured determinants of fracture healing and because most studies used a case–control design [30, 31]. One retrospective study in 19,731 patients with humeral fracture suggested that use of bisphosphonates doubled the risk for fracture non-union [32]. In this study, fracture non-union was defined as patients receiving an orthopedic intervention related to non-union 91–365 days after the initial fracture; it proved to be rare and occurred in 0.4% of the sample (81 cases, of whom 16% received a bisphosphonate after the fracture). Adjusted multivariable regression analysis suggested that use of a bisphosphonate in the postfracture period might be associated with an increased risk for non-union (OR = 2.37, 95% CI 1.13–4.96), though the conclusions of this study are limited by the small number of fractures and its cross-sectional design [32].

The clinical effect of oral bisphosphonate on osseointegration has been explored in trials in postmenopausal women with osteoporosis [33], in which patients with internal fixation of a pertrochanteric fracture were randomly allocated to alendronate 70 mg/week orally or control. The removal torque for the screws was two times higher in the treatment group, indicating improved osseointegration. Other studies with ibandronate and clodronate have shown that both systemic and local perioperative treatment with bisphosphonate can improve the fixation of total knee prostheses [34, 35].

There is an association between atypical subtrochanteric stress fracture and alendronate use [18]. The incidence of

this type of fracture is very low. Possible mechanisms include accumulation of microdamages, decreased repair, suppression of turnover, and increased mineralization.

In conclusion, there is RCT evidence that bisphosphonate treatment after the fracture does not delay fracture healing, even following hip-fracture surgery or when the drug is administered in the immediate postoperative period. Local or systemic application of bisphosphonate may improve osseointegration. The impact of bisphosphonates prior to fracture on fracture healing is unknown.

Denosumab

There has been one experimental study in animals of the impact of denosumab, the fully human monoclonal antibody against the RANK ligand (RANKL), on fracture healing [19]. Denosumab is a potent inhibitor of osteoclast-mediated bone resorption and would, therefore, be expected to have similar properties to the bisphosphonates. The effects of denosumab were therefore compared with those of alendronate in male huRANKL knock-in mice [19]. There was no effect of denosumab or the bisphosphonate on fracture union or initial callus formation in this animal model. Both agents were found to delay callus remodeling, though callus strength and stiffness were greater in treated animals than in controls [19]. The authors concluded that neither intervention had negative implications for short-term repair of fracture. To our knowledge, there are no studies on denosumab and osseointegration.

More recently, the effect of denosumab on fracture healing was tested in the FREEDOM trial, in the subset of 199 patients with incident nonvertebral fractures [36]. In this double-blind, placebo-controlled analysis, the use of denosumab was not associated with delayed healing or with any complications following fracture or surgical management, providing further support to the concept that even potent antiresorptive treatment does not interfere with fracture healing.

Selective Estrogen Receptor Modulators: Raloxifene

The effects of selective estrogen receptor modulators (SERMs) on bone repair, fracture healing, and osseointegration remain unclear. One experimental animal study in ovariectomized rats showed that raloxifene did not have an impact on progression of fracture repair [14], with similar radiographic assessments and biomechanical properties to sham-operated animals. Similar properties were found for estrogen. By contrast, a very recent study in a rat model of metaphyseal fracture indicated improved healing in osteoporotic bone with raloxifene and estrogen with regard to

callus formation, resistance, and elasticity [37]. On the basis of the limited nonclinical data available, we conclude that raloxifene (like estrogen) has a modest, if any, effect on fracture healing. To our knowledge, there is no clinical evidence for an impact of SERMs on bone repair.

Parathyroid Hormone

Agents with bone-forming properties would be expected to find applications in reconstruction of bone postfracture. The anabolic agent teriparatide (recombinant human parathyroid hormone [PTH] 1–34) is a potent anabolic agent that stimulates osteoblastic proliferation and differentiation, leading to an increase in bone mass. There is a large amount of experimental evidence for the impact of teriparatide on bone repair [38], and it is currently the only osteoporosis treatment for which an RCT in fracture healing has been completed.

Experimental Evidence

The first animal study of teriparatide in fracture healing was reported more than a decade ago by Andreassen et al. [39]. They induced a unilateral tibial fracture in intact rats administered teriparatide at the daily dose used in osteoporosis (60 µg/kg) or at a higher daily dose (200 µg/kg). After 20 and 40 days, the higher dose of teriparatide enhanced callus volume (+99% and +72%, respectively) and mechanical strength (ultimate load, +75% and +175%), while the lower dose had no influence at 20 days but increased callus volume (+42%) and mechanical strength (+132%) of the fractures after 40 days [39]. These changes were significantly different from vehicle at 20 and 40 days for the higher dosage of teriparatide (all $p < 0.01$) and at 40 days for the lower dosage (both $p < 0.01$) [39].

These experiments were followed by a large number of studies demonstrating that teriparatide increases callus formation and improves biomechanical strength of healing fracture in young and aged rats [40, 41], young male rats [42], ovariectomized rats [43, 44], and rabbits [45]. It was also shown to improve skeletal repair by enhancing external callus volume, total bone mineral content, bone mineral density (BMD), and cellular content of the callus [40–42, 44, 46].

Mechanistic studies in rats with a unilateral femoral shaft fracture indicate that teriparatide enhanced callus formation by the early stimulation of proliferation and differentiation of osteoprogenitor cells. The same workers detected increased production of bone matrix proteins and osteoclastogenesis during callus remodeling [42]. There is also evidence for an effect in the earliest stages of endochondral bone repair from a study in mice with closed

femoral fractures [47]. Treatment with teriparatide was associated with increased chondrocyte recruitment and rate of differentiation in the fracture callus, as well as increased callus volume. Expression of the Wnt-signaling genes was increased in teriparatide-treated mice, indicating that the effects of the agent are mediated, at least in part, by the Wnt-signaling pathways.

In the largest study of fracture repair performed in a rat model, 270 animals underwent closed femoral fracture followed by 5 or 30 µg/kg daily teriparatide or vehicle [46]. After 3 weeks, callus formation significantly improved in animals administered 30 µg/kg daily teriparatide, in terms of torsional strength, stiffness, bone mineral content, BMD, and cartilage volume (all $p \leq 0.05$ vs. control). After 5 weeks, all the animals had significant increases in bone mineral content, BMD, and total osseous tissue volume (all $p \leq 0.05$ vs. control) and decreases in void space and cartilage volume (both $p < 0.05$). Torsional strength was increased at 5 weeks in animals treated daily with 30 µg/kg ($p < 0.05$). Even though treatment with teriparatide was stopped at 5 weeks, there were sustained increases in torsional strength and BMD after 12 weeks in the 30 µg/kg group vs. controls (all $p \leq 0.05$). There was no change in osteoclast density, suggesting that teriparatide enhanced bone formation but did not induce bone resorption. The authors concluded that teriparatide enhances fracture healing by increasing mineralization, BMD, and strength throughout the remodeling phase of fracture healing [46]. This study was also instrumental in defining the lower effective dose of 5 µg/kg daily teriparatide.

Teriparatide has been demonstrated to enhance spinal fusion [48, 49]. Spinal fusion is used to manage spinal deformity or instability but can often result in pseudarthrosis. The impact of teriparatide on spinal fusion was investigated in a rabbit model [48] involving bilateral posterolateral spine fusion, followed by daily treatment with 10 µg/kg teriparatide ($n = 22$ rabbits) or saline only ($n = 22$ rabbits) for 6 weeks. At the end of the study, fusion was observed in 81% of the teriparatide-treated rabbits vs. 30% of controls ($p < 0.001$). Radiographic images for each L5–L6 spinal segment were scored using a five-point scale (0 = no bone, 5 = definite fusion), which showed an average score of 4.51 for teriparatide vs. 3.36 for control ($p = 0.001$) [48]. Histology and computed tomographic imaging showed more bone and cartilage in the treated than the untreated specimens.

The fixation of an orthopedic implant depends partly on the growth of bone at the interface (osseointegration), which may be promoted by a bone-forming agent. This has been explored for teriparatide in a study in which stainless steel screws were implanted in the tibia of rats receiving 60 µg/kg daily teriparatide ($n = 14$) or vehicle ($n = 14$) [50]. After 4 weeks of treatment, the removal torque of

screws implanted in the teriparatide animals was three times greater than in controls (3.5 vs. 1.1 Ncm, $p = 0.001$) and the pull-out force was more than doubled (145 vs. 66 N, $p = 0.002$). Histological analysis showed a greater density of trabecular bone around the implant with teriparatide. The results indicate that teriparatide may enhance osseointegration and the early fixation of orthopedic implants. A recent article has shown a remarkable potential of teriparatide as an adjuvant therapy for allograft repair in a mouse model of large femoral defect reconstruction [51].

Clinical Evidence

There are a growing number of case reports on the effects of teriparatide on fracture healing [52–54]. These report positive effects of teriparatide on healing in patients with hip fracture [54] or delayed union of a fracture of the spine or extremities [53]. There is also a report from an observational cohort of 145 patients with complicated fractures in a number of different anatomical sites (including spine and extremities) [38]. Treatment with 20 µg/day teriparatide was associated with resolution of pain or evidence of at least partial fusion within 12 weeks in 141 patients (97%).

There have been two randomized trials of teriparatide in fracture healing. One was a placebo-controlled, randomized, blinded, multinational trial in 102 postmenopausal women with a dorsally angulated distal radial fracture in need of closed reduction but not surgery. The patients were randomly allocated to receive placebo or 20 or 40 µg/day of teriparatide. The primary end point was the median time from fracture to first radiographic evidence of complete cortical bridging in at least three cortices. Median time to healing was 7.4 weeks with teriparatide 20 µg/day, 8.8 weeks with teriparatide 40 µg/day, and 9.1 weeks in the placebo group [55]. Whereas no significant difference between high-dose teriparatide (40 µg/day) and the control group could be detected ($p = 0.52$), post hoc analysis showed that the difference from placebo was significant for patients receiving teriparatide 20 µg/day (95% CI –2.7 to –0.6 weeks, $p = 0.006$). Another post hoc analysis excluded nine patients who did not meet inclusion criteria on blinded evaluation of radiographs. Again, in this new sample, there was no difference in time to healing between high-dose teriparatide and placebo ($p = 0.127$), but there was a significant difference between low-dose teriparatide and placebo (95% CI –2.8 to –1.2 weeks, $p < 0.001$) and low-dose vs. high-dose teriparatide (95% CI –2.7 to –0.4 weeks, $p < 0.03$) [55].

The finding of an effect for the lower, but not the higher, dosage was unexpected [55] and may simply illustrate the difficulties in carrying out RCTs in fracture healing. A subgroup analysis of callus formation on 5-week radiographs from 27 patients in one center indicated that

teriparatide may have a dose-dependent effect on callus formation [56]. The results suggest that radiographic quality at an early time point may be a sensitive variable, rather than time to cortical continuity [56].

The other RCT with teriparatide was a placebo-controlled study of osseous regeneration in 40 patients with periodontitis [57]. All patients underwent periodontal surgery and received either placebo or 20 µg/day teriparatide for 6 weeks. The primary end point was a radiographic linear measurement of alveolar bone level. After 12 months, patients treated with teriparatide had improved clinical outcomes, greater resolution of alveolar bone defects, and accelerated osseous wound healing in the oral cavity [57], with a mean linear gain in bone of 29% vs. 3% in the placebo group ($p < 0.001$). The authors concluded that teriparatide given in conjunction with periodontal surgery may be useful for the management of localized bone defects in the jaw [57].

In a prospective RCT, the effects of 100 µg/day of PTH(1–84) on pelvic fracture healing and functional outcome were evaluated in postmenopausal women. This treatment accelerated fracture healing, 7.8 vs. 12.6 weeks ($p < 0.001$), and improved the clinical outcome as evidenced a lower pain visual analog scale score and a better Timed Up and Go test [58].

In conclusion, there is clinical evidence for an effect of teriparatide in fracture healing. Anecdotal case reports cannot be considered as clinical proof, and interpretation of the RCT is hampered by the absence of an effect of the higher dose. However, the evidence is consistent with a positive impact of 20 µg/day teriparatide on clinical fracture healing and fracture non-union, and this is supported by the preclinical investigations which suggest a faster healing process with this agent. Further RCTs of teriparatide in fracture healing are clearly a priority.

Strontium Ranelate

There have been a number of experimental studies investigating the impact of strontium ranelate on bone repair, and there is some evidence for a clinical effect but no completed RCTs yet.

Experimental Evidence

Studies in animal models of fracture healing indicate that treatment with strontium ranelate is associated with improved bone microstructure, callus volume, and biomechanical properties [59–61], associated with a more mature and tightly arranged woven or lamellar bone after 2 months.

In one study, in ovariectomized rats with bilateral transverse osteotomy of the proximal tibiae [59], rats

treated with strontium ranelate (450 mg/kg daily) had higher BMD than controls (+28% at 4 weeks, $p < 0.01$, and +16% at 8 weeks, $p < 0.05$), and histology revealed that they also had increased bone formation and bone volume as well as improved microstructure. Although microcomputed tomography showed the fracture gap at 4 weeks had transformed into bony union at 8 weeks in all animals, those treated with strontium ranelate had more mature callus and a higher degree of mineralization at 8 weeks. These changes were associated with increases in the strength and stiffness of bone (+211% ultimate load and +75% stiffness vs. controls at 4 weeks, both $p < 0.01$) [59].

These observations have been confirmed in a rat model of osteoporosis, which demonstrated increased mechanical strength and fracture stiffness with strontium ranelate, again with more mature woven bone [60]. The difference was shown to be significant by histological grading, for which the 20 animals treated with strontium ranelate scored 8.0 ± 0.8 (grade 8 = entirely woven bone) and the 20 control animals scored 6.6 ± 2.2 (grade 6 = equal amounts of cartilage with some woven bone, grade 7 = predominantly woven bone with some cartilage) ($p = 0.038$ between groups). These workers also graded the callus radiographs using the Goldberg classification (stage 2 = possible union, stage 3 = complete union) and found higher scores for the strontium ranelate group than controls (2.7 ± 0.6 vs. 2.2 ± 0.7 , $p = 0.001$) [60].

There is one comparative study of strontium ranelate and teriparatide in 60 ovariectomized rats with a closed diaphyseal fracture [61] divided into four groups (strontium ranelate, $n = 15$; teriparatide, $n = 15$; no treatment, $n = 15$; and sham, $n = 15$). Strontium ranelate significantly improved the resistance of callus to torsional load after 4 weeks (+44%, $p < 0.05$ vs. ovariectomized rats), an effect less apparent with teriparatide (+20%, nonsignificant) [61]. Both treatments increased bone volume of the callus (+46% with strontium ranelate and +32% with teriparatide, both $p < 0.05$ vs. ovariectomized rats), but only strontium ranelate led to a significant increase in callus tissue volume (+32% with strontium ranelate, $p < 0.01$ vs. ovariectomized rats; +6% with teriparatide, nonsignificant).

These preclinical data support the concept of improved fracture healing with strontium ranelate. On the other hand, the results contrast with a study that failed to find any beneficial or harmful effects of strontium ranelate on traumatically induced fracture healing in intact rats [62].

Animal studies have also shown that strontium ranelate significantly improves implant osseointegration. One study in rats receiving strontium ranelate or vehicle for 8 weeks reported significant improvements in pull-out strength with strontium ranelate (+34%, $p < 0.05$ vs. control) [63].

Moreover, the bone surrounding the implant had improved biomechanical properties in both cortical (+12% modulus and +13% hardness) and trabecular (+7% modulus and +17% hardness) areas. Microarchitectural improvements comprised increased bone volume/total volume (+36%), trabecular thickness (+13%), and connective density (+23%) (all $p < 0.05$ vs. control) with a more plate-like structure and better bone-to-implant contact (+19%, $p < 0.05$) [63]. These effects were dose-dependent, with significant correlations between microcomputed tomographic results (trabecular parameters and bone volume/total volume) and biomechanical properties (push-out force) [64].

Clinical Evidence

There are several case reports supporting a beneficial impact of strontium ranelate on fracture healing and fracture non-union [65, 66] but no RCT evidence yet. One of these reports described two cases of apparent fracture healing with strontium ranelate in postmenopausal women with osteopenia or osteoporosis and previous delayed union [66]. There are also four cases of non-union of complicated long bone fractures for up to 20 months, which had all failed to respond to conventional management, including internal and/or external fixation [65]. Treatment with strontium ranelate for between 6 weeks and 6 months appeared to facilitate the consolidation of these fractures. These case reports need to be interpreted with some caution; however, they do underline that the influence of strontium ranelate in fracture healing merits further investigation in controlled trials.

Future Agents and Bone Repair

There is no clinical evidence for an impact on bone repair for any of the agents currently in development for the management of osteoporosis. There is experimental evidence for some of these agents, notably sclerostin antibody and DKK1 antibody. On the other hand, bone morphogenetic proteins (BMPs) were developed to directly promote bone healing.

The protein sclerostin is secreted by osteocytes and acts as a negative regulator of osteoblasts and bone formation. Sclerostin antibody has been shown to induce an increase in bone formation and bone mass and strength without an impact on resorption [67]. In view of its anabolic mode of action, sclerostin antibody is currently in phase 2 development for the treatment of conditions with low bone mass and fracture healing. It has been tested in a variety of experimental models of bone healing, and preliminary results support a positive impact of the agent on fracture repair and

gap defects. There is one report of a study on the regeneration of traumatized metaphyseal bone in rats, in which sclerostin antibody enhanced implant fixation with significant differences in pull-out strength at 2 and 4 weeks vs. control (38% and 56%, respectively; both $p < 0.005$) [68]. The authors concluded that sclerostin antibody improves mechanical fixation of cancellous bone and suggested that this implies a general ability to form more bone, rather than a specifically improved response to fracture. Further research is likely to elucidate whether these preclinical results will translate into clinical applications.

A number of targets on the Wnt-signaling pathway are currently being tested for therapeutic applications in the management of osteoporosis [69]. There are no clinical data on fracture healing, though the preclinical data have revealed some interesting points. For example, experiments in a transgenic mouse model demonstrated that β -catenin levels are low in intact bone tissue but remain high during the entire period of fracture repair, with the cellular levels depending on time after fracture [70]. Many Wnt ligands were expressed during fracture healing and appear to play a major role. Treatment with DKK1 (an antagonist of the Wnt/ β -catenin pathway) impaired β -catenin signaling and fracture healing, while mice expressing an activated form of β -catenin in osteoblasts showed markedly enhanced bone healing. Interestingly, treatment with lithium

activated β -catenin in the healing fracture, though healing was enhanced only when lithium treatment was started subsequent to fracture [70]. The possibility that lithium could improve fracture healing is intriguing, though the implications of the timing of administration need further investigation. In this context, the effect of treatment with another agent modulating Wnt signaling has also been reported to depend on timing of treatment initiation. A study in LRP5 knockout mice reported that DKK1 antibody enhanced fracture repair when it was administered immediately after fracture but not when it was administered after a further 4 days [71].

Growth factors can stimulate one or more steps in endochondral and intramembranous bone formation. The potential of BMPs has been the subject of a large amount of research, and they are commercially available for local administration [4]. The effect of local administration of BMPs was the subject of a recent Cochrane review including 11 RCTs [72]. Apart from one study, time to tibial fracture healing was comparable between the BMP and control groups. There is some evidence for increased healing rates vs. usual care in acute tibial fracture (risk ratio [RR] = 1.19, 95% CI 0.99–1.43) but no evidence for beneficial effects in patients with non-union (RR = 1.02, 95% CI 0.90–1.15) [72]. The role of BMP in fracture non-union remains unclear, and further research is necessary.

Table 1 Effect of currently available osteoporosis treatments on bone repair

Agent	Effect on bone repair	
	Experimental evidence	Clinical evidence
Bisphosphonates	Increased callus size and mineralization	Retrospective data, but not RCT data, indicate increased risk for delayed healing
	Reduced callus remodeling	Impact of use prior to fracture on fracture healing unknown
	Improved mechanical strength	One large RCT does not show any impairment in fracture repair
	Improved implant osseointegration	Local and systemic application may improve implant fixation
Denosumab	Delayed remodeling	Post hoc analysis of one RCT showed no effect on fracture healing
	Improved callus strength and stiffness	
SERMs	Modest improvement in callus formation, resistance, and elasticity	None
Teriparatide	Increased callus formation	Case reports suggest benefit on fracture healing
	Increased callus volume, mineralization, and cellular content of callus	RCT in patients with distal radial fractures demonstrated a benefit for 20 $\mu\text{g}/\text{day}$ (but not 40 $\mu\text{g}/\text{day}$) on radiographic healing
	Improved biomechanical strength, including torsional strength and stiffness	RCT in patients with severe chronic periodontitis showed a benefit of teriparatide along with periodontal surgery on alveolar bone
	Improved implant osseointegration	
Strontium ranelate	Improved callus resistance and volume	Case reports suggest benefit on fracture healing
	Improved bone microarchitecture	
	Improved biomechanical properties, including strength, stiffness, and ultimate load	
	Improved implant osseointegration	

BMD bone mineral density, *RCT* randomized controlled trial, *SERM* selective estrogen receptor modulator

Conclusion

The evidence for the effects of osteoporosis drugs on bone repair and fracture healing is overall positive. Experimental studies indicate that teriparatide and strontium ranelate may have a favorable impact on fracture repair, and there are signs that these effects may potentially translate into therapeutic applications. There is no evidence that short-term treatment with the antiresorptive agents (bisphosphonates, SERMs, or denosumab) is detrimental to fracture repair, though the impact of long-term therapy is unknown. The effects of currently available osteoporosis agents in terms of experimental and clinical evidence for bone repair and fracture healing are summarized in Table 1.

Despite promising results, there remain a number of issues for the research agenda for fracture healing in osteoporosis. First, there is a paucity of epidemiological data on fracture healing and complication rates in patients with osteoporosis, which hampers measurement of pharmacological effects. Accurate epidemiological study of fracture, osteoporotic or otherwise, is difficult due to widely differing coding systems between hospitals and variations in the criteria for good functional outcome [73]. Delayed union appears to be likely in 5–10% of cases. The risk of non-union is increased by local factors, such as poor contact, biomechanical instability, and the magnitude of the injury, as well as a number of systemic conditions (e.g., osteoporosis, diabetes, or NSAID use). Further research is therefore needed to provide more accurate data on epidemiology as well as the natural course of the disease [8, 9]. In this context, more research is also necessary into the impact of delayed fracture healing on health economics and the cost-effectiveness of treatment, for example, a measure of the economic impact of a patient spending less time in hospital due to pharmacological fracture healing.

Second, it is proving extremely difficult to transpose the plethora of promising results in small animal models to humans. This may be related to a number of factors. For example, many of the animal models are in normal bone and not in osteoporosis. Moreover, osteopenia is not osteoporosis, ovariectomy is not menopause, and cortical bone is mechanically different from cancellous bone. Better understanding of how the mechanical and biological processes work could lead to improved definition of animal models as well as boundary conditions and, possibly, new therapeutic targets.

Third, some of the results suggest that the timing of administration may play an important role in the pharmacological management of fracture. This is most likely due to the large number of pathways involved in the phases of bone repair and should be explored in greater depth to resolve questions surrounding when the treatment might best be administered.

Finally, surgical decisions and expertise could markedly change the impact of pharmacological treatment, particularly if the treatments affect both fracture healing and orthopedic fixation with screws. This issue is closely tied to the quantitative evaluation of fracture healing in RCTs [11]. A related problem is difference in the impact on bone repair for differing fracture sites (e.g., radius, tibia, or hip) or bone types (cortical or cancellous bone). There are currently no guidelines on whether results at one site can be extended to all others. This is an important point given the relative difficulties in recruiting patients with very serious fracture into RCTs.

In conclusion, drugs and bioactive substances will probably have a role in the future management of fractures. There is currently no evidence that osteoporosis treatments have a negative effect on bone repair and some experimental evidence for positive effects on healing, notably for agents with a mode of action that involves bone formation. There is an urgent need for better RCT evidence of an impact of osteoporosis treatments on fracture repair.

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