Orthopaedic surgeons’ strategies in pharmacological treatment of fragility fractures

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Summary

Fragility fractures are the most severe complications of osteoporosis and the poor mechanical properties of bone can make fixation and healing of these fractures extremely difficult. The role of orthopaedic surgeons does not end in skillful fixation of the fractures, but they have the unique opportunity to prevent complications which can negatively affect the patient’s quality of life. The best practice for preventing the risk of further fractures in patients presenting fragility fractures includes fall prevention, investigation of possible causes underlying osteoporosis, attention to exercise, calcium and vitamin D supplementation as well as prescription of drugs. Actually two classes of agents can be used for their effect on fracture prevention: antiresorptive and bone forming agents. Systemic therapy reduces the risk of vertebral (30-70%) and non-vertebral fractures (12-53%), depending on agents and patients’ compliance. Preclinical and clinical studies have shown that pharmacological agents involved in osteoporosis can also influence the phases of fracture repair. Preclinical studies and evidences from case reports showed a positive effect of anabolic drugs on bone healing and implant osseointegration. The interventions in the process of fracture healing had evolved from a diamond to a pentagon concept, with interactions between the mechanical environment, the local therapies, the vascularity of the fracture site, the biology of the host and the systemic therapy which has the potential to represent the fifth interaction factor. The orthopaedic surgeon plays a central role in clinical setting to evaluate the efficacy of systemic anti-fracture drugs for improving fracture repair and preventing complications.

KEY WORDS: anabolics; bisphosphonates; bone healing; fracture; osteoporosis; prevention.

Introduction

Bone fractures are the most serious complication of osteoporosis and preventing new fractures is the basic goal of osteoporosis treatment. Orthopaedic surgeons are often the first and may be the only physicians to evaluate patients with fragility fractures, so they play an important role to ensure that preventive, surgical and pharmacological measures are implemented. Their role does not end in skillful fixation of the fractures, but they have the unique opportunity to prevent complications of fragility fractures. The best practice for primary and secondary prevention of fragility fractures includes fall prevention, investigation of possible causes underlying osteoporosis, attention to exercise, calcium and vitamin D supplementation as well as prescription of antiresorptive and anabolic drugs. The first role of orthopaedic surgeon consists of preventing the risk of further fractures in older patients presenting fragility fractures. Interventions to reduce the recurrence of falls can be an effective preventive strategy but calcium supplementation and antiresorptive pharmacological therapy showed a real efficacy to reduce the incidence of future fractures. Overall, preventive pharmacotherapy reduces the risk of vertebral (30-70%) and non-vertebral fractures (12-53%), depending on agents and patients’ compliance. The effect on non-vertebral fractures is lower and it depends on the different fracture sites. The poor mechanical properties of osteoporotic bone can make fixation and healing of fracture extremely difficult. The outcome of bone healing can be affected by several drugs: steroids, chemotherapy drugs, and some classes of antibiotics have been reported to exert a negative effect on bone healing (1). The possibility of positive effect on fracture healing with specific pharmacological agents would be an important advance in reducing osteoporosis-associated morbidity. Pharmacological agents may influence the process of fracture healing with effects on the reparative and remodeling phases (2). This review looks at the preclinical and clinical evidence of how these agents may affect the prevention of new fractures and bone healing.

Surgical treatment

Although an association between osteoporotic bone and a higher risk of non-union is still debate, to reduce this complication the orthopaedic surgeon must know the current guidelines to treat the fragility fractures. There is often only one
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chance to manage the fracture accurately (one-shot surgery). Fast skillful surgery with minimal tissue injuries is desirable and dedicated implants for osteoporotic bone and tissue engineering techniques like growth factors, bone grafts, calcium phosphate ceramics can be used to increase efficacy of surgical treatment. The diamond concept of bone fracture healing includes the mechanical environment, the tissue engineering, the vascularity of the fracture site and the biology of the host taking in consideration such as genetic predisposition as well as pre-existing co-morbidities (3).

Diet

Advice on diet is important because older patients are at risk of vitamin D and calcium deficiency. For patients older than 50 years of age, the recommended daily intake of calcium is 1200 mg and 800 UI of vitamin D. In patients with fragility fracture, calcium and vitamin D supplementation may not be sufficient, and treatment with antiresorptive or anabolic medication should be considered.

Pharmacological treatment

Actually two classes of agents are available for their effect on fracture prevention and fracture healing: antiresorptive and bone forming agents. Orthopaedic surgeons play a central role in the choice of the best systemic therapy for improving fracture repair and preventing complications.

Bisphosphonates

Bisphosphonates are the most common medications prescribed to treat osteoporosis. They are able to prevent fragility fractures by suppression of bone resorption by osteoclasts, decreasing the rate of bone remodeling. The efficacy of bisphosphonates for fracture risk reduction is well established in several clinical studies. For instance, in a Cochrane review (2011) Wells et al. presented what we know from research about the effect of alendronate for preventing osteoporotic fractures. Eleven trials representing 12068 women were included in this review and the authors observed that alendronate 10 mg daily produces both clinically important and statistically significant reductions in vertebral (45%), non-vertebral (23%), hip (53%) and wrist fractures (50%) for secondary prevention (4).

In another Cochrane review (2008) Wells et al. presented the effect of risedronate for preventing osteoporotic fractures. The authors included in this review 7 trials representing 14049 women and they observed that risedronate 5 mg daily produces both clinically important and statistically significant reductions in vertebral (39%), non-vertebral (20%) and hip fractures (26%) for secondary prevention (5).

Current controversies exist on the usefulness of bisphosphonates on fracture healing. In fact, as suppressors of bone resorption, they play a central role in the remodeling phase of fracture healing. Moreover, recent published studies show the presence of atypical subtrochanteric fractures in patients receiving long-term treatment with bisphosphonates (6).

Many studies have been performed in animal models of fracture healing using different bisphosphonates, including alendronate, risedronate, zoledronic acid, pamidronate and in-cadronate. Most studies have shown that the administration of bisphosphonates is associated with an increase in callus size and mineralization or a neutral effect (7). Furthermore, some studies suggest that the treatment with bisphosphonates enhance screw fixation (8). By contrast, some animal studies have reported that bisphosphonates delay callus remodeling and the removal cartilage, so they may delay the fracture-healing process (9).

Results from a double-blind, randomized controlled trial indicate that bisphosphonate treatments do not affect the rate of fracture healing or the incidence of complications, and there is no association between timing of administrations and risk for delayed fracture repair (10).

Further studies are needed to determine the effective role of bisphosphonates on fracture healing for their application in clinical practice but current data demonstrate that bisphosphonates mustn’t be interrupted in patient when fragility fracture occurs.

Denosumab

Denosumab (DMAB) is the fully human monoclonal antibody against the RANK ligand (RANKL). By inhibiting RANKL, DMAB prevents the development and activity of osteoclasts, thus decreasing bone resorption and increasing bone density. This is associated with fracture prevention at multiple sites. The anti-fracture efficacy of 60 mg denosumab given subcutaneously every 6 months has been evaluated in post-menopausal osteoporotic women in an international phase III clinical trial known as the FREEDOM trial. After 3 years, there was a 68% reduction in the incidence of new vertebral fractures. The incidence of non-vertebral fractures was reduced by 20% and of hip fractures by 40% (11).

An experimental study in animals compared the effects of DMAB with those of alendronate on murine fracture healing. Investigators reported that both agents delayed callus remodeling, but this did not diminish the mechanical integrity of the healing fractures in mice receiving these treatments. In contrast, strength and stiffness were enhanced in these treatment groups compared with control bones (12).

The effects of DMAB on fracture-healing was also evaluated in the FREEDOM trial. In this study, non-vertebral fractures were reported for 386 patients in the DMAB group, and for 465 in the placebo group; surgical treatment was required for 79 and 120 fractures, respectively. DMAB did not seem to delay fracture-healing or contribute to other complications, even when it is administered at or near the time of the fracture (13).

Strontium ranelate

Strontium ranelate is absorbed on the surface of the bone and it partially replaces the calcium in the apatite crystals, without changing the bone crystal characteristics. It has a dual mode of action on bone with a decoupling between the formation of bone and its resorption, increasing the action of osteoblasts and reducing that of osteoclasts. In the SOTI trial, Meunier et al. enrolled 1649 postmenopausal women with at least one prevalent osteoporotic vertebral fracture. Strontium ranelate at dose of 2gr/day has shown to reduce the risk of new vertebral fractures by 33% over 4 years of treatment compared with placebo; in patients
with two or more previous fractures risk reduction was 36% over 4 years (14). Reginster et al. conducted the TROPOS trial and enrolled 5091 postmenopausal osteoporotic women with one or more prevalent fractures. Patients were randomized to receive Strontium ranelate 2 g/day or placebo for 5 years. Strontium ranelate has shown to reduce the risk of nonvertebral fractures by 15% over 5 years versus placebo. 1128 women were classified at high risk of hip fractures and in this subgroup strontium ranelate has reduced the risk of hip fractures by 43% in 5 years (post hoc analysis) (15).

In experimental study in ovariectomized rats with proximal tibiae fracture, administration of strontium ranelate promoted fracture healing, increasing callus, bone mineral density and biomechanical strength at early period of fracture healing (4 weeks post fracture) (16).

Regarding the use of strontium ranelate on fracture repair in humans there are only reported clinical cases that indicate a potential benefit. Tarantino et al. reported their experience in a woman with a fracture of distal radius and ulna and in another woman with a fracture of the base of the fifth metatarsal. Patients were treated with strontium ranelate 2 g/day and the fracture treme disappeared after 90 days and 40 days of treatment respectively. Strontium ranelate has demonstrated the propensity to promote fracture healing with a clinical improvement due to pain relief and functional recovery in patient with non-union or delayed union fracture (17). Alegre et al. reported four cases, in patients of both sexes, of fracture non-union for up to 20 months. The use of strontium ranelate 2 g/day for between 6 weeks and 6 months appeared to contribute to bone consolidation and suggested a potential beneficial effect on fracture healing (18).

Parathyroid hormone

Parathyroid hormone (1-84) has a central role in calcium homeostasis, maintaining serum levels within physiological limits by stimulating bone resorption. Teriparatide, 1-34 fragment of parathyroid hormone (PTH), is administered daily as a subcutaneous injection. It stimulates osteoblastic proliferation and differentiation, leading to an increase in bone mass.

Neer et al. reported a randomized controlled trial conducted in 1637 postmenopausal women with prior vertebral fractures. PTH 1-34 at doses of 20 µg and 40 µg daily reduced by 65 and 69% respectively, the risk of one or more new vertebral fractures compared with placebo. Women treated with 20 µg and 40 µg of PTH 1-34 were also 53 and 54%, respectively, less likely to have one or more new nonvertebral fragility fractures than the women in the placebo group (19).

In animal models parathyroid hormone has been shown helpful to accelerate the bone healing, increasing the endochondral mineralization of fracture repair (20). Peichl et al. reported a prospective, randomized controlled study on effect of PTH 1-84 versus placebo on the time of fracture-healing in elderly women with osteoporosis and pelvic fracture. After 8 weeks of treatment with once-daily injection of 100 µg of PTH 1-84, all pelvic fractures were completely healed (21).

In an experimental study in rats with tibial fractures the intermittent administration of high dose (200 µg/Kg/day) of PTH 1-34 treatment enhanced callus volume and mechanical strength of fractures after both 20 and 40 days of healing. Lower dose, 60 µg/Kg/day, of PTH 1-34 had no influence on the fracture healing after the first 20 days, but after 40 days it resulted a substantial increase in the volume of the bone callus and mechanical strength of the fractures (22). Aspenberg et al. conducted a prospective, randomized, double blind study of 102 postmenopausal women with distal radial fracture treated non-operatively. Women were randomized in a pharmacologic treatment with teriparatide 20 µg, teriparatide 40 µg or placebo within 10 days of fracture for 8 weeks. Post hoc analyses revealed that teriparatide 20 µg determines median time to healing significantly shorter than placebo group, and no significant difference between teriparatide 40 µg and placebo group (23).

There are also clinical cases about the effect of PTH 1-34 on fracture healing. Brunemann et al. reported cases of two women with periprosthetic fractures of femur and a man with a non-union of fracture of the radius treated with teriparatide, 20 to 60 µg/day by subcutaneous injection for 6-10 weeks. The radiographic results have demonstrated that teriparatide can induce consolidation in non-unions and delayed healing of bone fractures (24).

**Future agents: sclerostin antibody, DKK1 antibody**

The Wnt pathway plays an important role in bone formation and regeneration. Sclerostin and Dickkopf-1 (DKK1), Wnt signaling proteins, are potent inhibitors of bone formation. Studies in various animal models of bone disease have shown that inhibition of sclerostin using a monoclonal antibody increases bone formation, density, strength and improves bone healing in models of bone repair. Similar studies in animal models have shown that DKK1-Ab increases bone formation and improves implant fixation and fracture repair. Clinical trials are ongoing to evaluate the effects of ScI-Ab and DKK1-Ab in humans for the treatment of bone loss and for bone repair (25).

**Conclusions**

The role of orthopaedic surgeons does not end in the surgical treatment of the fracture; but they should also ensure better pharmacological management of secondary prevention of osteoporotic fractures. The best management of patients with fragility fractures can only be achieved with coordinated and multidisciplinary team-work where the orthopaedic surgeons keep up to date with current guidelines to treatment of osteoporotic fractures (26).

There are some promising experimental and clinical evidence that anti-fracture drugs may potentially improve fracture healing in osteoporotic patients (Table 1). Anabolic drugs have also a positive effect in osseointegration of implant. Maimoun et al. demonstrated that strontium ranelate increases mechanical fixation of implant with a positive effect on microarchitecture of the bone surrounding implant (27).

Our experience in the treatment of periprosthetic femoral fractures reported good clinical results at one year follow-up in a small case series included 5 patients with average age of 77 years. The use of an anabolic drug (teriparatide or strontium ranelate) started within 7 days after surgical treatment has...
accelerated the fracture healing with an average of clinical and radiographic union of 3 months (28).

However, further studies should be performed for better randomized controlled trial evidence of an effect of pharmacological agents on fracture healing.

In conclusion, the trauma and orthopaedic surgeons play a central role in the treatment of patients with osteoporotic fractures. Increased awareness of the responsibility and the opportunity to improve surgical techniques and implant choice, as well as a better systemic pharmacological treatment are required to achieve a significant impact on this important clinical problem.

The interventions in the process of fracture healing had evolved from a diamond to a pentagon concept where the systemic therapy has the potential to represent the fifth interaction factor (29).

Declaration of interest
Nothing to declare.

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