

Accelerated fracture healing with teriparatide

Consolidação de fratura acelerada com teriparatida

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SUMMARY

Satisfactory healing of the osteoporotic fracture is critically important to functional recovery, morbidity, and quality of life. Some therapies for osteoporosis may affect the processes associated with bone repair. For example, bisphosphonates in experimental models are 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. For the osteoanabolic agent teriparatide, case reports and a randomized trial have produced mixed results, but they are consistent with a positive impact of teriparatide on fracture healing. Some of the agents currently being developed for osteoporosis, notably sclerostin and DKK1 antibodies have shown a beneficial effect on fracture healing. At this point, therefore, there is no evidence that osteoporosis therapies are detrimental to fracture healing with some promising experimental evidence for positive effects on healing, notably for those agents whose actions are primarily anabolic. *Arq Bras Endocrinol Metab.* 2013;57(2):153-6

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SUMÁRIO

A consolidação adequada da fratura osteoporótica é essencial para recuperação funcional, morbidade e qualidade de vida. Alguns tratamentos para osteoporose podem afetar os processos associados ao reparo ósseo. Por exemplo, os bisfosfonatos, em modelos experimentais, estão associados com aumento do tamanho do calo e a mineralização, reduzindo o remodelamento do calo e melhorando a força mecânica. Tratamento com bisfosfonato, local ou sistêmico, pode melhorar a fixação de implantes. Não foi observado impacto negativo na consolidação da fratura, mesmo após uma cirurgia maior ou quando administrado imediatamente após a fratura. Relatos e um estudo randomizado com o osteoanabólico teriparatida produziram resultados mistos, mas que são consistentes com o impacto positivo da teriparatida na consolidação da fratura. Algumas das drogas que estão sendo desenvolvidas no momento para osteoporose, como anticorpos para esclerotina e DKK1, têm mostrado efeito benéfico na consolidação da fratura. No estágio atual, portanto, não há evidência de que terapias para osteoporose impeçam a consolidação da fratura, mas existem algumas evidências experimentais promissoras de efeito positivo na consolidação, especialmente daqueles agentes cuja ação é primariamente anabólica. *Arq Bras Endocrinol Metab.* 2013;57(2):153-6

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INTRODUCTION

The end result of osteoporosis is fragility fracture. The subsequent bone repair occurs in 3 stages: inflammatory, reparative, and remodeling. Initial trauma provokes an inflammatory response, involving the release of a variety of substances including fibronectin, growth factors, fibroblasts, endothelial cells, and osteoblasts,

which together help fill the fracture site with granulo-matous 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.

Management of the osteoporotic fracture remains a major challenge in orthopedics (1). Whether a fractured osteoporotic bone requires more healing time and whether risk of nonunion is greater are points still under debate (2). Other points related to the surgical procedures *per se*, which could delay the healing process, are noteworthy. For example, internal fixation of the osteoporotic fracture can fail with rates ranging from 10% to 25% (3).

Any pharmacological intervention that improves the reparative process, implant fixation, and in the end, overall fracture healing, would therefore constitute a considerable advance in helping to reduce osteoporosis-associated morbidity. Indeed, while the main goal of osteoporosis treatment is to prevent fracture – and progress has certainly been made in this regard – another goal should be to facilitate fracture healing.

Based on animal and some clinical data, teriparatide [PTH(1-34)] appears to accelerate fracture healing (4,5). The doses employed to facilitate fracture healing, however, have been higher than those needed to increase bone mineral density (BMD), and to reduce fracture risk in human subjects. Reports of accelerated fracture healing with teriparatide have stimulate even further interest (6).

A noteworthy example comes, from our own experience. An 84-year old woman sustained a fall-related transtrochanteric fracture classified as a Tronzo IV fracture (Figure 1). Two years prior to the fracture, BMD by dual-energy X-ray absorptiometry (DXA, GE Lunar, Madison WI) revealed T-scores of -2.4 and -2.2 at the lumbar spine and total hip, respectively. No secondary causes of bone loss were apparent, historically, biochemically or in hormone measurements. Her past history was noteworthy for treatment with a SERM, but it was discontinued 2 years prior to the fracture. Two days after the fracture, surgical intervention consisted of fixation with a cephalomedullary implant (Trochanteric Femoral Nail: TFN, Synthes). One month after surgery, X-rays revealed no evidence for fracture healing because the callus could not be seen (Figure 2). The patient could not ambulate easily because of severe hip and generalized skeletal pain. Teriparatide, 20 mcg daily, was started on the 31st post-operative day. After only 1 month of teriparatide treatment, radiograph of right femur showed obvious dense callus formation (Figure 3), and the patient became fully ambulatory.



Figure 1. Radiograph of left femur before surgery.



Figure 2. Radiograph of left femur 30 days after surgery. No bone callus was seen.



Figure 3. Radiograph shows the dense bone callus after 31 days of teriparatide 20 mcg/day.

DISCUSSION

An attractive concept associated with agents that build bone, such as osteoanabolic drugs, is that they might be used to facilitate fracture healing. To this point, teriparatide has been shown to accelerate fracture repair (7,8) and, in fact, has been studied in a randomized clinical trial (6).

Andreassen and cols. reported the first animal study of teriparatide in fracture healing more than a decade ago (9). After a unilateral tibial fracture was induced in rats, teriparatide was administered at two different daily doses, 60 or 200 µg/kg. Twenty and 40 days thereafter, the higher dose of teriparatide significantly ($p < 0.01$) enhanced callus volume (+99% and +72%, respectively) and mechanical strength (ultimate load, +75% and +175%, respectively). The lower dose required 40 days of exposure to demonstrate significant ($p < 0.01$) improvement in callus volume (+42%) and mechanical strength (+132%) (9).

Fracture healing occurs in three distinct stages. The first is inflammatory, the aftermath of the physiological consequences of injured tissue. The bleeding, for example, leads to a hematoma, and then to a fibrin network around the fracture site. A number of proteinaceous growth factors and cytokines are then released into the area, a process that takes about one week. Following this acute phase, a longer second step initiates fracture repair. At the site of the hematoma, a callus forms. The formation of callus requires that osteoblasts be recruited into the region. This process is the step requiring osteoanabolic input both for reparative cytokines and the cells that participate in this process. It is this step that determines the pace and extent to which healing will proceed. Finally, the remodeling phase replaces the calcified callus with lamellar bone which ultimately becomes incorporated into the actual fracture site and its local milieu. This final reparative stage helps to account for slow strengthening of the fractured bone, a process that may take months, and perhaps even years, to complete. The duration of fracture healing is highly variable, depending in part on individual reparative capabilities, the location of the fracture, and the degree to which mechanical loading takes place.

The second phase of fracture healing is the point at which teriparatide may have important actions. Several case reports have documented the positive effects of teriparatide on fracture healing (10-12). These reports include salutary effects of teriparatide on healing

of hip fracture (12), as well as stimulating healing of delayed unions of the spine or an extremity (11). An observational cohort of 145 patients with complicated fractures in a number of different anatomical sites (8) identified positive effects of teriparatide (20 µg/day) on the resolution of pain, or evidence of at least partial fusion within 12 weeks in 141 patients (97%).

Two randomized trials testing the efficacy of teriparatide in accelerating fracture healing have been conducted. One was a placebo-controlled, randomized, blinded, multinational trial in 102 postmenopausal women with 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 endpoint 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 (16). 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 the lower, 20 µg/day of teriparatide (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 newly defined 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, $p < 0.03$) (6). Since the primary endpoint of the study was defined by the high dose, and not the lower dose results of teriparatide, the significance associated with the lower dose could not be considered to be conclusive.

Another randomized clinical trial with teriparatide was a placebo-controlled study of osseous regeneration in 40 patients with periodontitis. All patients underwent periodontal surgery and received either placebo or 20 µg/day teriparatide for 6 weeks (13). The primary endpoint 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, 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 might be useful for the management of localized bone defects in the jaw.

In a prospective randomized clinical trial, the effects of 100 µg/day of the full length form of parathyroid hormone, namely PTH(1-84), on pelvic fracture healing and functional outcome were evaluated in postmenopausal women (14). PTH(1-84) accelerated fracture healing, 7.8 vs. 12.6 weeks ($p < 0.001$), and improved clinical outcome measures: lower pain in the visual analog scale score, and better Timed Up and Go test (14).

A new class of osteoanabolic therapy targets sclerostin, an inhibitor of bone formation, by an anti-sclerostin antibody. Sclerostin is expressed in osteocytes and exerts its effect by means of an inhibitory effect on osteoblasts, whereby bone formation is reduced (15,16). By blocking sclerostin, an osteoanabolic effect is achieved. Li and cols. (17) showed that exposure of the antisclerostin antibody in a rat model increased bone formation, mass, and strength. In addition, bone formed under the influence of the antisclerostin antibody was not lost in the early period after disuse (17). Further studies are needed to determine more definitely the effects of this novel osteoanabolic agent on fracture healing.

In conclusion, the early data with teriparatide provide results that suggest that this osteoanabolic agent may be effective in accelerating fracture healing as well as stimulating the healing process in those patients whose healing is delayed, or in which there is non-union. Data are promising both with regard to those with osteoporosis and others whose fractures have occurred under traumatic conditions.

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