Fracture healing and drug therapies in osteoporosis

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Summary

Fracture repair has not been fully optimised and there is opportunity to increase the healing rate and reduce the number of complications using pharmacological means. While most anti-osteoporosis drugs have been widely tested for their ability to decrease the risk of osteoporotic fractures, fragility fractures still occur in patients under medical intervention. The primary purpose of this systematic review is to understand these underlying mechanisms between bone and drug therapies in osteoporosis and the overall promotion of fracture healing and callus formation. Databases such as MEDLINE, Google Scholar, EMBASE and CINAHL were searched and nine articles met all inclusion criteria. We report that there is still large controversy and a need for clinical trials to address the deficiencies found in animal models. There is no clear evidence yet as to whether complications during the course of healing are attributable to implant anchorage problems in osteoporotic bone or to possibly delayed healing in the aged.

KEY WORDS: fracture, healing, osteoporosis, drug therapies, callus formation, elderly.

Introduction

Fracture repair involves the proliferation and differentiation of several tissue types in a sequence, followed by remodelling. Drugs could potentially influence all these processes. Some drugs can have an effect on the proliferation of early callus, while others affect the differentiation of chondrocytes or osteoblasts, capillary formation or sensitivity to mechanical input. Because the repair of fractures has not been fully optimised, it is possible to enhance it using pharmacological or other means such as ultrasound or electromagnetism (1-3). Noninvasive methods in fracture treatment such as systemic injections have also been examined such as L-dopa which has been reported to enhance early fracture healing and nonunions (4, 5). The interaction between drugs and fracture healing and its effect on callus formation are still issues of debate. A preliminary report on the effects of daily subcutaneous injections of parathyroid hormone in a rat closed fracture model showed an increase in callus area and strength and histological analysis resulted in the amount of new bone (6). This is an emerging field as several pharmaceutical companies are currently working on new principles for stimulation of fracture repair, which would in turn reduce clinical and socioeconomic problems associated with fracture healing.

Most anti-osteoporosis drugs have the ability to decrease the risk of osteoporotic fractures; however, fragility fractures still occur in patients under medical intervention. For this reason, the safety and efficacy of most anti-osteoporosis drugs for fracture healing have been evaluated in order to decide whether they should be ceased or continued after fracture. It is expected that the anti-osteoporosis drugs have the ability to promote fracture healing at the same time. The primary purpose of this systematic review of the current literature is to tease out these subtleties between drugs and fracture healing and evaluate the potential for non-invasive methods to enhance fracture repair and callus formation in the aged with osteoporosis.

Methods

A literature search was conducted by a librarian using a keyword search with terms such as "osteoporosis" and in combination with "fragility fractures" and "callus formation" or "bony callus." The search was limited to articles concerning controlled in vivo and clinical trials that used pharmaceutical therapies in order to modify fracture healing. This way pharmaceutical therapies were considered a therapeutic intervention in prospective cohort studies using models linked (directly or indirectly) with non-unions and not as a diagnostic or prognostic tool for prospective or retrospective studies. In other words, all the selected studies evaluated the direct use of pharmaceutical therapies administered in various ways, for fracture healing alone or in combination with other substances or growth factors.

Exclusion criteria were set and the following were included: articles using language other than English, articles that were not experimental controlled trials (reviews, letters, and expert opinion publications). Furthermore, this search focused only on osteoporosis and thus excluded other mechanisms of bone metabolism such as distraction osteogenesis, and osteonecrosis. We excluded, cytostatics, antibiotics such as fluoroquinolones and corticosteroids and Cox inhibitors (NSAIDS) as these are known to impair fracture healing and is beyond the scope of the present systematic review. Articles that conformed to our criteria were retrieved and then all the articles related to these were searched.

Results

A total of 3, 680 hits were found across different database searches such as Medline from 1996 to 2009 (Week 1), Google Scholar, Pubmed, EMBASE, and CINAHL. In total 57 articles were selected and retrieved in full. Finally, nine articles were selected by two reviewers who judged the articles on meeting the inclusion criteria (Table I).

Table I - List of articles included in our systematic review on fracture healing and drug therapies and its effect on callus formation.

Author (last name, year)	Study design	Sample size	Intervention type	Drug administration type	Conclusions	Callus formation (+/-)
McDonald M., et al. 2008 Amanat N., et al. 2008	Animal study	Wistar rats (n=272 male)	A 1.1 mm Kirschner wire was inserted into the medullary canal of the femur	Control Group: weekly subcutaneous injections of saline (1 ml/kg). Zoledronic Acid (ZA) Single Bolus ZA Group: subcutaneously ZA 1 week post fracture (0,1 mg/kg) Weekly ZA dose Group: 5 doses at 0.02 mg/kg/week	At 6 weeks: both ZA treatment groups fracture callus peak increased, 20% for bolus ZA, 31% for weekly ZA. At week 26: callus peak torque increased with ZA treatment to the saline (88% bolus ZA, 96% weekly ZA)	Increased
Morgan E.F., et al. 2008	Animal study	New Zealand rabbits (n=64 female)	Partial thickness osteotomy was created in the lateral left distal tibial metaphysic and filled with Tricalcium phosphate (TCP).	4 groups: 1) BMP-7 and PTH, 2) BMP-7, 3) PTH, and control.	Combined treatment with rhBMP-7 and PTH enhanced healing through improvements in callus structure, organization, and mechanical function. The combined treatment resulted in higher torsional rigidity, higher strength, and more extensive bone formation both within the surrounding tissues and in the defect as compared to the control group.	Decreased
Holstain JH., et al.2008	Animal study	38 SKH1-Hr mice (30-40 g body weight)	The right femur of each animal was fractured by a 3-point bending device and stabilized using a locking nail.	Daily intraperitoneal (i.p. injection of rapamycin from the day of fracture	At 5 weeks rapamycin-treated animals revealed an increase in callus diameter, whereas the size of the callus in vehicle-treated controls was found decreased at this late time point. Thus, the difference in callus formation between the two groups observed at 2 weeks had disappeared by 5 weeks	Delayed
Wang JW., et al. 2007	Animal study	130 2-month-old female Sprague-Dawley rats with initial body weight of 178-201 g. All the rats were randomly subjected to either OVX (n=120) or sham surgery (n=10).	All the OVX rats were used to establish open fracture models and fixed with intermedullary nails. Transverse open fracture model was made in the proximal one-third of the right tibia.	Simvastatin or vehicle drugs were injected subcutaneously to the fracture site once on the day of fracture and twice in 5 days thereafter. A solution of 5% simvastatin (Hisun Pharmaceutical Co. Ltd. China) simvastatin was diffused in PBS with 2 dimethylsulfoxide and 0.1% BSA. Each injection contained 5 mg/kg simvastatin of the SVS group and an equal volume (about 30 μl-50 μl) of vehicle solution to the vehicle groups.	Substantial histological differences between the OVX + vehicle and OVX + SVS callus zones were visible at 1 and 2 weeks after treatment. The callus cross-section area in simvastatin-treated rats was significantly enlarged by 21.3% at 1 week (20.22 ± 3.42 mm^2 vs. 16.67 ± 4.02 mm^2) and by 21.5% at 2 weeks (23.63 ± 3.25 mm^2 vs. 19.45 ± 3.19 mm^2) than the vehicle group	Increased

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Author (last name, year)	Study design	Sample size	Intervention type	Drug administration type	Conclusions	Callus formation (+/-)
Moroni A., et al. 2007	Clinical study	16 female patients with a pertrochanteric fracture in osteoporotic bone.	Fractures were fixed with a pertrochanteric fixator and four 6/5-mm-diameter hydroxyapatite-coated tapered pins	Group A patients: 70-mg oral ALN dose/wk Group B: Control or no therapy	The combined mean extraction torque (and standard deviation) of the pins implanted at positions 1 and 2 (cancellous bone) was 2558 ± 1103 N/mm in Group A and 1171 ± 480 N/mm in Group B. The combined mean extraction torque of the pins implanted at positions 3 and 4 (cortical bone) was 4327 ± 1720 N/mm in Group A and 4075 ± 1022 N/mm in Group B. Weekly systemic administration of alendronate improves pin fixation in cancellous bone in elderly female patients with osteoporosis. We observed a twofold increase in extraction torque with the pins implanted in cancellous bone.	Increased
Cebesoy O., et al. 2007	Animal study	Forty-two male Wistar rats randomized into two groups .	Left tibiae of all animals were broken in closed manner using a manual three-point bending technique through mid-tibia .The fractures were not stabilized internally. External stabilization was done with the use of a cast. The animals in each group were further divided into smaller groups (three rats in each) and put to separate cages. They were exposed to light and dark in periods of 12:12 h without any restriction of mobilization.	Group 1 = 450 mg/kg Strontium Ranelate (SR) starting from the first post-operative day. Group 2 = Control. The animals were sacrificed on the 2nd, 3rd and 4th post-operative week (each week 7 animals were sacrificed) and the broken tibiae were removed.	Radiological analysis: No significant difference was found in callus formation and bone union. Histopathological analysis: fractures healed normally in both groups as weeks advanced. However, when both groups were compared, no significant difference was found in terms of fracture healing.	No significant differences
Kakar S., et al. 2007	Animal study	C57BL/6 mice (male)	Closed unilateral femoral fractures (right)	Daily systemic injections of saline (control) or 30 micro gr/kg PTH for 14 days after fracture	Fixation and standard histological analysis: visible increase in callus size and apparent bone density by day 14 and approaching bridging by day 21 in response to PTH. PTH-mediate enhancement of fracture repair is primarily associated with an amplification of chondrocyte recruitment and maturation in the earliy fracture callus	Increased
Meyer Ra., et al. 2003	Animal study	Female Sprague-Dawley rats	Closed midshaft femoral fractures were created in six-week-old and one-	BMP-2	All genes studied were up-regulated by the fracture in both age-groups. Thus, the failure of the older rats to	Slower healing in older age group

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Author (last name, year)	Study design	Sample size	Intervention type	Drug administration type	Conclusions	Callus formation (+/-)
			year-old, and killed at zero-time (unfractured) or at 0.4, one, two, three, four, or six weeks after the fracture. mRNA levels were measured by reverse transcription polymerase chain reaction in the fracture callus for twenty-seven matrix, cytokine, and cytokine-receptor genes for the seven animals per time-point per age-group.		heal promptly was not due to the lack of expression of any of the studied genes. The increase in mRNA for Ihh and BMP-2 in the older rats was smaller than that in the younger rats, which may contribute to slower fracture repair. The return of mRNA gene expression to baseline in the older rats prior to healing may contribute to the delayed union. The slower healing response of the older rats did not stimulate a negative-feedback increase in the mRNA expression of stimulatory cytokines.	
Skripitiz R, et al. 2001	Animal study	Sprague-Dawley rats, (n=28) Screwed in either one proximal tibia (n = 8) used for the measurement of removal torque; screwed in both (n = 20) proximal tibiae: one for removal torque (left) and the other (right) for pull-out strength.	In the medial proximal tibial metaphysis an insertion hole was hand-milled in the cancellous bone, approximately 3 mm distal to the epiphysis, using a regular 1 mm injection needle. Each implant was inserted in the hole and screwed down carefully until its head reached the bone. All the screws were manufactured from stainless steel (SS 2333). The threaded part was 1.7 mm in diameter and 3 mm long	PTH was administered in a dosage of 60 [mu]g/kg/day (n = 14) or vehicle (n = 14) over a period of four weeks. At the end of this time, the degree of fixation was assessed by measuring the removal torque on one screw in each rat (n = 28) and the pull-out strength on the contralateral screw (n = 20).	PTH increased the mean removal torque from 1.1 to 3.5 Ncm and the mean pull-out strength from 66 to 145 N . No significant differences in body-weight or ash weight of the femora were seen. Histological examination: both groups had areas of soft tissue at the implant-bone interface, but these appeared less in the PTH group. These results indicate that intermittent treatment with PTH may enhance the early fixation of orthopaedic implants.	Increased

We did include 4 articles which looked at callus formation without drugs in fracture healing for further comparison (Table Ia).

Discussion

Fracture healing in animal models

Although many studies have shown that ovariectomy (OVX) has a pronounced influence on bone mass and metabolism, the properties of healing fractures in diseased models such as osteoporosis have received little attention. Only recently has the clinical importance of osteoporotic fractures led to more exploration of information from osteoporotic animal models. Hao et al. established an osteoporotic fracture rat model to evaluate the changes of microstructure and mineralized tissue of newly formed callus during the middle and late phase of fracture healing in both normal and osteoporotic rats induced by OVX (48 Sprague Dawley rats at 8 months old were ovariec-tomized, and 48 were used as controls) (7). Twelve weeks after OVX, osteoporosis was confirmed by total body areal bone mineral density (aBMD) measured using dual-energy X-ray absorptiometry. Established OVX rats was defined as a significantly lower mean aBMD than that obtained from the control group. A controlled mid-shaft femoral fracture was made and the rats were sacrificed at 4, 8 and 12 weeks. The scanned specimens included the original cortical diaphyseal bone as well as the entire periosteal and endosteal callus with diameters ranging from 4.20 to 7.95 mm (µCT-40, Scanco Medical, Basserdorf, Switzerland). After 12 weeks of OVX, aBMD in the OVX rats was on average 19.4% less than that in the controls (P<0.01). Volumetric BMD increased healing over time in both the treated group (OPF) and the control group (NF). The BMD in the OPF group was lower than that in the NF group at all post operation time points, which was found statistically significant at 8 weeks and 12 weeks. The callus area in the OPF group was smaller than that in the NF group at 4 weeks after fracture (P<0.05). Thereafter, the callus area increased in both groups. However, the callus area in the OPF group was not on

Table Ia - List of articles included in our systematic review on fracture healing without drug therapies and its effect on callus formation.

Author (last name, year)	Study design	Sample size	Intervention type	Conclusions	Callus formation (+/-)
Hao Y. et al., 2007	Animal study	Sprague-Dawley rats (n=96, female). OPF group (OVX) n=48 NF group (Control) n=48	A mid-shaft femur fracture model was established 12 weeks after OVX. Femurs were harvested at 4, 8 and 12 weeks for peripheral quantitative computed tomography (pQCT), micro-computed tomography (MicroCT), histology and biomechanical test.	MicroCT data (12 wks) showed the total callus, bony callus, and newly formed bone was approximately 20% lower in the OPF group than that in the NP group, and the total connectivity was 56% lower in the OPF group as compared to the NF group. Biomechanical test data, at 12 weeks, showed that the failure load of the left femur of OPF group was 17% less compared to that of the NF group (Pb0.01), and 15% lower bending stiffness (Pb0.05), 20% lower bending stress (Pb0.01), and 28% lower energy at failure (Pb0.0 were observed in the OPF	Decreased
Lill C.A., et al 2003	Animal study	Swiss Mountain sheep (14 female) Group 1: 7 osteoporotic sheep. Group 2: 7 healthy animals (controls).	A mid-shaft osteotomy of the right tibia fracture (gap of 3 mm). To avoid an effect of bone healing due to the corticosteroid, the medication was stopped 90 days before osteotomy. Bending stiffness and torsional stiffness of the callus zone were also determined.	Callus area, callus density, and osteoporosis status were determined at 0, 4, and 8 weeks using peripheral quantitative computed tomography. The increase of in vivo bending stiffness of the callus was delayed approximately 2 weeks in osteoporotic animals. A significant difference (33%) in torsional stiffness was found between the osteotomized and contralateral intact tibia in osteoporotic animals, but no significant difference occurred in normal sheep (2%). In osteoporotic animals, ex vivo bending stiffness was reduced (21%). Bending stiffness was correlated with callus density; torsional stiffness was correlated with callus area and to a lesser extent with callus density. This study demonstrated a delay of fracture healing in osteoporotic sheep tibiae with respect to callus formation, mineralization, and mechanical properties.	Delayed
H. Namkung-Matthai, et al. 2001	Animal study	34 female Sprague-Dawley rats, aged 2 months, ovariectomized or sham operation (sx). Ovx rats were fed LCD to induce rapid osteoporosis, whereas sx rats were fed conventional food	An open right femoral midshaft fracture was created and stabilized by intramedullary pins in rats from both ovx and sx groups (517/gp)	Biomechanical data from the healing femur of the ovx rats revealed a fivefold decrease in the energy required to break the fracture callus, a threefold decrease in peak failure load, a twofold decrease in stiffness and a threefold decrease in stress as compared with the sx group. Histomorphological analysis: revealed a delay in fracture callus healing with poor development of mature bone in the ovx rats.	Decreased
Kubo T., et al. 1999	Animal study	Wister rats (n=90 female) ovariectomized (n=15) sham-operation (n=10) 30 rats each from the OVX+F group and the control-F group were used for examinations and the remaining 10 rats were used for examination	A transverse fracture on the diaphysis produced by a lateral longitudinal incision on the unilateral femur Maintained a low calcium diet	Femur fracture was produced 12 weeks after ovariectomy, and the healing process was monitored for the subsequent 12 weeks. As a result, the healing rate was 100% in all animals. Bone fracture itself can be healed even under such conditions as low bone mineral density, low estrogen and low calcium	Increased

Table II - The increase or delayed callus formation with respect to various drug therapies.

Agent	Principle mode of action	Affect on fracture healing
Bisphosphonates	Anti-catabolic	Increase callus size Increased strength or no change in animal models Delay remodelling
SERMs	Anti-catabolic	Minimal effects noted
Strontium ranelate	Anti-catabolic Anabolic?	Unknown
PTH	Anabolic	Increase cartilage production Increased rate of remodelling Increased strength in animal models

average 21% larger than that in the NF group until 12 weeks after fracture (P<0.01).

In animal models, fracture healing takes longer in older animal (8, 9). In a study by Meyer et al., the investigators demonstrated that the rat model showed slower healing in the elderly in a comparison study of a 6-wk old vs 1-yr old rat with a closed, nailed femoral shaft fracture (10). The young healed in 6 weeks showing periosteal bridging, while the old needed 26 weeks. However, the BMD was not considered and there was no ovariectomy. The investigators demonstrated the same pattern of cytokine gene expression in both groups, with lower levels of IHH and BMP-2 in older rats. The levels fall back to normal at the same time in both groups, despite the fact that the older rats had not healed. There is no feedback loop to keep the cytokine drive going. Whether ovariectomy adds an additional impediment is conflicting. Some animal studies showed deficient healing, especially in the early response (11-15) and some did not (16-20). Differences in the timing of ovariectomy, age of the animals and dietary factors make comparisons difficult.

Fracture healing in the clinical scenario

Clinical observations indicate that fragility fractures heal despite the abnormality of bone remodelling in osteoporosis. There is no clear evidence yet as to whether complications during the course of healing are attributable to implant anchorage problems in osteoporotic bone or to possibly delayed healing in elderly patients.

Most patients who need treatment for osteoporosis will currently receive anti-catabolic agents and it is important whether this may have any disadvantage for the healing of incident fractures in the long term. Anabolic agents that are used to treat osteoporosis would be expected to have a beneficial effect on fracture healing (Table II). There is no evidence that anti-catabolic drugs impair restoration of mechanical integrity, irrespective of when they are given or their mechanism of action, despite the fact that they may delay remodelling (21).

The fracture healing potential in patients with compromised bone structure and turnover can be explained by the different pathways of fracture repair and bone remodelling.

Fracture repair involves different stages of tissue differentiation which resemble aspects of embryological skeletal development (22). Opinion on the role of osteoclasts in fracture repair is conflicting. Whereas the initial inflammatory phase and subsequent bone formation during the repair phase are largely osteoclast independent, coupled remodelling of woven bone to lamellar bone during the remodelling phase at the end of fracture repair does depend on osteoclast activity.

The initial drive to the periosteal bone regeneration is weak in older people, and switches off before healing occurs. Slower (endosteal) healing modes will heal the fracture eventually, given stability. But stability depends on enduring fixation and enduring fixation is difficult in osteoporotic bone.

Implant fixation

Although the fracture healing potential in the osteoporotic patient is normal, the incidence of fracture nonunions and malunions is significant. This is in part due to implant loosening occurring prior to the completion of the fracture healing process. This complication is caused by the inability of standard implants to achieve good and durable fixation in the mechanically weak bone. The difficulty in obtaining stable fixation is responsible for the less than satisfactory clinical results which are commonly seen with this patient population (23).

The causes of pin loosening and infection are multifactorial. Biomechanical tests have shown that implant anchorage is impaired in osteoporotic bone in animal studies, implants failed earlier in compromised bone structure, via cut-out or cut-through, than they did in healthy bone. Thermal and mechanical damage of the bone during pin insertion and formation of fibrous tissue at the bone-pin interface have been identified as the most important factor in pin loosening (24-26). This fibrous tissue formation is thought to be an inevitable phenomenon with stainless steel and titanium pins. However, differences in bone-pin contact related to different metal types have been reported. A higher osteointegration was reported in pins coated with titanium compared with similar pins made of stainless steel.

Another innovative approach is to use osteoporosis drugs which can improve implant fixation. Despite the large numbers of patients treated with bisphosphonates, the effect of these drugs on fracture healing has not been extensively investigated in humans (27). The achievement of adequate fracture stability, which promotes rapid bone repair, is also necessary. This was shown in a variety of animal experiments using different types of systemic or locally applied bisphosphonates (28). Bisphosphonates attracted to the hydroxyapatite in the bone will firstly inhibit bone resorption by being incorporated selectively into osteoclasts and secondly, by interfering with the cells' biological activity. Previous animal studies have shown that bisphosphonates can improve early fixation in both cortical and cancellous bone (29). Other studies have also demonstrated that alendronate inhibits bone resorption at the bone-screw interface thereby enhancing fixation (30). This active bone remodelling initiated by the alendronate around the implant permits good bone-screw fixation and the prevention of pin loosening or infection. This effect has been reproduced in humans utilizing an external fixator and hydroxyapatite screws for the treatment of

proximal femur fractures. The data showed that weekly systemic administration of alendronate improved pin fixation in cancellous bone in elderly female patients with osteoporosis. There was a twofold increase in extraction torque with the pins implanted in cancellous bone (31). Furthermore, there were no differences in clinical outcomes, such as fracture healing or loss of fixation between the control and those treated with alendronate.

Improved implant anchorage was also achieved in animal experiments using PTH (32). So far no clinical data are available that support these findings in humans. The reproduction of findings from animal experiments in clinical studies is complicated by the fact that no universally accepted measure of fracture healing exists in humans. Alternatively, the rate of prospectively defined bone-related complications, or measurement of function and radiological status at defined time points of healing, might be utilized (33).

Drugs that improve fracture healing

Bisphosphonates

Recent studies with incandronate, showed an enlarged callus that was strong, but incandronate delayed callus remodelling in the fractured femora of rats (34-36). This delay persisted 49 weeks after fracture. Some suggested that the strength of the callus is paramount and that the delay in resorption of the callus is of little consequence, because the organism compensated for any negative effect of the drug on composition of the callus by increasing size (37). However, others have suggested that fracture healing is considered complete when the fracture line is no longer visible radiographically, when the skeletal architecture is restored, and when the mechanical strength is fully restored (38, 39).

Parathryoid hormone

Although constantly increased levels of PTH lead to bone resorption, it has been known since the 1930's that intermittently administered PTH has a strong positive effect on skeletal metabolism (40).

Parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) signal through a common receptor PTHR1, and it has been hypothesized that systemic PTH regulates endochondral bone formation by altering the local PTHR1-Indian hedgehog (IHH) regulatory loop. In the growth plate, this pathway has been shown to coordinate chondrocyte and osteoblast proliferation and differentiation, which appears consistent with the same function in fracture repair (41). Additionally, regulatory interactions in the growth plate have shown that IHH signalling is coordinated with canonical WNT signalling during endochondral bone formation. The role of the WNT signalling pathway in fracture repair has attracted recent attention. This interest initially stemmed in part from observations that gain and loss-of-function mutations of one of its co-receptors, lipoprotein-related peptide 5 (LRP5), result in a gain or loss of bone mass, respectively, and the disease osteoporosis pseudoglioma syndrome (42). Additionally, WNT pathway members and target genes, such as the WNT target gene WNT-induced secreted protein 1 (WISP1), are expressed during fracture healing (43, 44). There are eighteen identified murine WNTs, which are divided into canonical and noncanonical classes on the basis of their functional ability to form a secondary embryonic body axis (45). While the non-canonical WNT signalling pathway is not clearly understood, the canonical pathway has been studied widely in relation to endochon-

drol bone formation, including its role in regulating mesenchymal progenitor lineage selection, osteogenesis, and chondrogenesis (42). Recent studies have further evaluated the possibility of enhancing fracture repair through the pharmacological activation of the canonical WNT pathway.

Kakar et al. evaluated the mechanisms by which systemic PTH (PTH [1-34]) affects fracture repair (42). With use of a closed murine femoral fracture model, bones were harvested at periods throughout healing following injections with 30 µg/kg PTH or saline solution for fourteen days after fracture. The authors found a threefold greater increase in chondrogenesis relative to osteogenesis over the course of repair, with earlier appearance of chondrocyte hypertrophy in the PTH-treated calluses. Furthermore, PTH treatment significantly induced an increased level of canonical WNT-signaling in PTH-treated bones, suggesting that the effects of PTH administration occur at least in part through WNT signalling. It is even at these lower doses of PTH administration of this study and that of other animal studies that have shown an enhancement in bone repair (46, 47).

Conclusions

Mechanical and biological factors contribute to the healing processes of bone and are affected by age and osteoporosis. Callus formation is the natural repair and fixation response to a fracture in the absence of artificial fixation devices including casts or osteosynthetic materials. Callus response is also an expression of fracture healing and by quantifying the increase in size of the callus it is possible to measure the healing process. Animal studies have shown that ovariectomy significantly reduces bone mass. The mechanical strength of the bone following bridged healing indicates a reduction in the completion of healing. In this situation, fracture healing appears to be delayed with respect to callus mineralization and biomechanical properties. There are a variety of effects noted with current standard anti-resorptive therapies in common use for the treatment of established osteoporosis. Limitations exist with animal models and more clinical evidence is needed in order to evaluate these treatments for callus formation in the aged with osteoporosis.

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