Chapter 2
Fracture Repair and Bone Grafting
Chuanyong Lu, MD Eric Meinberg, MD Ralph Marcucio, PhD Theodore Miclau, MD

Biology of Bone Repair
Fracture healing involves a highly integrated sequence of events through which bone is restored to its preinjured condition. The events that occur during healing have been classically divided into four phases: inflammation, soft callus, hard callus, and remodeling (Figure 1). Initially, during the inflammatory stage, a hematoma forms in response to the trauma, and the inflammatory cells in the hematoma debride the wound and may help recruit cells that facilitate repair. As skeletal progenitor cells are recruited and begin to differentiate into osteoblasts and chondrocytes, the hematoma is slowly transformed into a soft callus composed primarily of cartilage. At this time, osteoblasts form a collar of bone adjacent to the fracture gap. After this initial period of stabilization, chondrocytes undergo a maturation process, the matrix becomes calcified, osteoclasts remove the calcified cartilage, and endothelial cells invade the cartilage. The soft callus becomes a hard callus as bone forms behind the invading vasculature. Once formed, the bone is remodeling until the skeletal injury has been completely repaired and the bone marrow cavity has been restored.

The Inflammatory Phase
Inflammation plays a key role in the initiation of fracture repair. During the inflammatory stage of repair, numerous lymphocytic cells, including macrophages, neutrophils, and degranulating platelets, infiltrate the fracture site and release cytokines, which include platelet-derived growth factor (PDGF), tumor necrosis factor β (TGF-β), interleukins 1, 6, 10, and 12 (IL-1, IL-6, IL-10, and IL-12), and tumor necrosis factor α (TNF-α). Some of these cytokines are detected at the fracture site as early as 24 hours postinjury and are important for the expansion of the inflammatory response by acting on a variety of cells in the bone marrow, periosteum, and fracture hematoma.

Inflammatory molecules may directly regulate bone healing. In the absence of TNF-α, both endochondral and intramembranous ossification are delayed during repair, suggesting that this molecule plays an important role in the induction of osteochondro-progenitor recruitment and differentiation. The inactivation of cyclooxygenase-2 (COX-2), the enzyme required for the production of prostaglandins, a metabolite of arachidonic acid metabolism, has been shown to delay mesenchymal cell differentiation into the osteoblastic lineage during fracture healing via the repression of runx-2 and osterix, two important transcription factors for osteoblast differentiation. In addition, suppression of the inflammatory response through the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to impede fracture repair by inhibiting COX enzymes. Recently, leukotrienes, another metabolite of arachidonic acid, have been implicated in the repair process. Treatment of animals with either montelukast sodium or zileuton, which either block signaling or inhibit production of leukotrienes, respectively, stimulates chondrocyte proliferation during fracture healing in animal models.
The Soft Callus Phase
Following injury, mesenchymal cells aggregate and form condensations at the site of the fracture in response to growth factors and cytokines that are present. During this early stage of repair, stem cells differentiate into chondrocytes or osteoblasts depending on the mechanical environment. In general, mechanical instability favors chondrocyte differentiation and endochondral ossification, whereas mechanical stabilization favors osteoblast differentiation and intramembranous ossification. During endochondral ossification, cells condense and differentiate into chondrocytes. Production of cartilage provides stabilization of the fracture site, and bone eventually forms to replace the cartilage template. In contrast, during intramembranous ossification, mesenchymal cells condense and osteoblasts dif-
differentiate in these condensations in conjunction with invading endothelial cells that establish a blood supply. Clinically, the primary mode of healing is via endochondral ossification, but intramembranous ossification occurs simultaneously to varying degrees, depending on the extent of mechanical stability.

The Hard Callus Phase and Remodeling
During the healing process, the soft callus is slowly transformed into a hard callus via the process of endochondral ossification. Chondrocytes in the fracture callus produce a cartilaginous matrix and undergo a maturation process that eventually leads to their terminal differentiation into hypertrophic chondrocytes. The process of terminal differentiation is complex and involves the interplay of several signaling molecules and pathways, including Indian hedgehog (Ihh), parathyroid hormone–related peptide (PTHrP), fibroblast growth factors (FGFs), and bone morphogenetic proteins (BMPs). During development, these molecules pattern the growth plate in the developing endochondral skeleton and coordinate the timing and location of chondrocyte proliferation, maturation, hypertrophy, and terminal differentiation. These molecules and pathways all are candidates for stimulating repair after injury.

Throughout the process of chondrocyte maturation, the chondrocytes release proteases (such as mmp13) that degrade the extracellular matrix, and express angiogenic factors such as vascular endothelial growth factor (VEGF). Eventually the cartilage becomes calcified at the junction of the maturing chondrocytes and the newly formed bone. The chondrocytes then undergo apoptosis, the extracellular matrix is degraded, and new blood vessels invade the interface. The newly formed woven bone then undergoes remodeling through organized osteoblast and osteoclast activity, eventually forming bone that is indistinguishable from the adjacent skeletal tissues.

Source of Stem Cells During Fracture Repair
There are multiple sources of stem cells during fracture healing, which include the periostium and endosteme, the bone marrow, the adjacent muscles, and the circulatory system. Recent evidence suggests that the major source of cells that form the cartilage and bone during fracture repair are derived from the periostium and endosteme, with a potential contribution from the bone marrow. Although bone marrow–derived mesenchymal stem cells may be an adequate source of cells for tissue engineering, the role of endogenous mesenchymal stem cells in fracture healing appears to be minimal.

Factors Affecting Bone Healing
A variety of factors must be considered when clinically treating a patient with a fracture or nonunion. Some of these factors, such as the severity of injury or patient comorbidities, cannot be altered, whereas others can be treated or manipulated to improve the rate of union and eventual outcome. Optimization of these different factors, including patient-specific factors and medications, may prove useful in achieving bone union.

Patient Factors
There are a variety of known patient-related variables that affect fracture healing. Often, multiple comorbidities are found in a single patient and may act synergistically to decrease the union rate and ultimate clinical outcome. Additionally, as the population ages, individuals are living longer and have more medical problems, which present further challenges to the treating physician.

Nutritional deficiencies, especially abnormalities in vitamin D and calcium, have long been associated with impaired fracture healing. Patients with unexplained nonunions who have undergone thorough endocrinologic assessment have been found to have associated metabolic or endocrine abnormalities that have not been previously diagnosed. In one study, 84% of patients referred for management of a nonunion were found to have a metabolic abnormality, and 68% were found to have a vitamin D deficiency. Animal studies have also demonstrated the impact of protein malnutrition on fracture healing and enhancement of fracture union by means of a high-protein anabolic diet. To date, the impact of protein supplementation on fracture and wound healing has been poorly studied in humans.

Gastric bypass surgery, used increasingly for the management of morbid obesity, has profound effects on bone metabolism. The Roux-en-Y procedure, the most commonly performed bariatric procedure, bypasses the duodenum, the primary site for calcium absorption. This results in calcium and vitamin D deficiency, upregulation of parathyroid hormone, and increased calcium resorption. These patients require calcium and vitamin D supplementation. Unlike those who undergo the Roux-en-Y procedure, patients who have a gastric banding procedure do not develop secondary hyperparathyroidism because the small intestine is not bypassed.

Smoking has been long associated with delayed fracture union and increased risk of non-union. Nicotine inhibits tissue differentiation and the angiogenic response in early stages of fracture healing, and interferes with osteoblast function. In one study, grade I open tibial shaft fractures took 69% longer to heal in smokers than in nonsmokers. A significantly higher rate of nonunion in Ilizarov reconstruction has also been reported. Whenever practical, patients should be counseled to stop smoking to improve fracture healing.

Diabetes mellitus, in addition to its many associated complications and comorbidities such as neuropathy and peripheral vascular disease, is known to affect fracture healing. Lower extremity fractures in patients with diabetes have been shown to take approximately 1.6 times as long to heal than in control subjects who do not have diabetes, whereas an ankle fracture in pa-
tients with Charcot arthropathy can take up to 3 months longer to heal than in those patients with protective sensation. This is thought to be caused by decreased cellularity of the fracture callus, delayed endochondral ossification, and decreased strength of the callus. In animal studies, this pathway can be reversed with normalization of blood glucose with insulin, suggesting the importance of careful glycemic control in clinical practice.

Because of the success of antiretroviral drugs, HIV can now be considered a chronic disease with a long-term asymptomatic phase. Patients with HIV have been noted to have a higher prevalence of osteopenia, osteonecrosis, and fragility fractures, as well as delayed bone and wound healing. Many factors, including antiretroviral medications, intraosseous circulation, and derangement in cytokines such as TNF-α have been implicated. Patients also tend to have poorer nutrition and a reduced body mass index, further complicating bone healing.

**Medications**

The use of bisphosphonates in treatment is increasing as osteoporotic fractures are being recognized as a major public health problem. Although bisphosphonate treatment significantly decreases the incidence of osteoporotic fractures in the spine and hip, long-term bisphosphonate use may be associated with some side effects. Bisphosphonates inhibit the ostoclastic resorption of bone, therefore slowing remodeling and, possibly, bone healing. Recent radiographic studies have demonstrated a longer time to union in surgically treated wrist fractures and an increased rate of nonunion in humerus fractures. It has been suggested that while healing time is increased, ultimate bone density and callus strength is improved. Long-term bisphosphonate use may be associated with higher risk of atypical subtrochanteric and femoral shaft fractures. However, due to the low incidence of these atypical fractures, larger scale clinical studies are needed to further establish a causal relationship.

Systemic long-term administration of corticosteroids inhibits fracture healing and callus strength in animal models. Increased complications have been reported in clinical studies, including a 6.5% higher rate of nonunion of intertrochanteric hip fractures compared to that of control models. In addition to steroids, NSAIDs have been associated with prolonged healing time due to their antiprostaglandin action. Animal data suggest that COX-2 selective NSAIDs have a similar negative dose-dependent effect on bone healing and should be avoided in the early stages of postfracture care.

**Enhancement of Fracture Healing**

Many physical and biologic methods have been developed to enhance fracture healing. Some are widely used clinically, such as bone grafting and the placement of BMPs, whereas others are still in their early stages of development.

**Bone Grafting**

**Autogenous Bone Grafts**

Autogenous bone grafting continues to be the gold standard for treating osseous defects and stimulating new bone formation. Autogenous bone grafts have osteoconductive and osteoinductive properties, and can provide osteogenic cells, which are important for early bone formation. Autogenous cortical bone grafts can provide mechanical support with limited capability to supply osteoblasts. Most of the osteocytes in a cortical bone graft will die after grafting, and the nonviable bone will be slowly replaced by creeping substitution. Creeping substitution is a slow process that may take years to complete, and in many instances may never be fully accomplished. Autogenous bone grafts can be harvested from the anterior or posterior iliac crests, or local metaphyseal regions during a procedure. Harvesting of autogenous bone grafts is associated with a significant risk of complications, such as persistent pain at the surgical site; the amount of bone graft that can be harvested is limited. Therefore, efforts have been made to develop different bone graft substitutes.

**Allografts**

Allografts are harvested from donor cadaver tissue, thereby avoiding the complications associated with autograft harvesting. Allograft bone is available as cancellous, cancellous/cortical morcellized chips, or structural cortical grafts. Allografts have both osteoconductive and osteoinductive properties, but their osteoinductive capacity is limited in comparison with that of autografts. In addition, allografts do not provide viable osteogenic cells; therefore, their ability to form bone is not as good as that of autografts. Regular processing of allografts includes physical débridement of soft tissue, a wash with ethanol to remove blood and live cells, and gamma irradiation to sterilize the bone tissues. Processing, especially gamma irradiation, has a significant influence on the performance of allografts. High doses of irradiation, which may help kill bacteria and viruses, impair the biomechanical properties of allografts by causing splitting of polypeptide chains or radiolysis of water molecules. Irradiation may also affect the osteoconductive and osteoinductive capacities of allografts in a dose-dependent manner.

Demineralized bone matrix (DBM) is a special form of allograft. It is prepared by acid extraction of allograft bone. DBM retains bone collagenous and noncollagenous proteins, including BMPs, and has both osteoinductive and osteoconductive properties. Because of demineralization, DBM has better osteoinductive capacity than regular allografts. In some reports, comparable capacity for bone formation has been observed between DBM and autogenous bone graft 35, suggesting DBM may be a suitable alternative and supplement to autogenous bone graft. There are several commercially available DBM products that are used clinically to improve spinal fusion, graft fracture nonunions, and fill bone defects. However, the efficacy of DBM varies due to different processing methods. The age of the donor
is not a factor that significantly affects the efficacy of DBM.^{37}

Because allografts are harvested from donors, safety issues such as disease transmission are of major concern. Although harvesting techniques and thorough sterilization are important, strict donor screening is essential for reducing the risk of disease transmission. The American Association of Tissue Banks (AATB) has adopted a protocol for strict screening of tissues, and its program of accreditation has put many tissue banks under its oversight, which helps improve the safety of bone allografts. As a result, it is believed that the actual magnitude of viral transmission from allografts is very low, with estimates of less than 1 in 1 million procedures.

**Synthetic Bone Substitutes**

Synthetic bone substitutes were developed as an alternative to autografts and allografts. Their compositions include calcium sulfate, calcium phosphate, tricalcium phosphate, and bioglass. They are available in different forms, including powder, pellet, or putty, and can be used as implant coating or bone defect filler. Synthetic bone substitutes are osteoconductive, but not osteoinductive. Several clinical studies (level I evidence) have shown that using calcium phosphate–based bone substitutes may allow for bone defect filling, early rehabilitation, and prevention of articular subsidence in distal radius and tibial plateau fractures.^{38-40} Level II evidence suggests that calcium sulfate is a safe and effective bone substitute.^{41} The current trend is to develop different tissue engineering approaches and make composites from synthetic bone substitutes with collagen, DBM, growth factors, bone marrow cells, or mesenchymal stem cells to improve their osteogenic potential.

**Platelet-Rich Plasma**

Platelets play an important role in the inflammatory response after bone injury. Activated platelets release many growth factors, including PDGF, TGF-β, and VEGF. The effectiveness of platelet-rich plasma (PRP) in fracture healing has been tested in both animal experiments and clinical trials. In a rat diabetic fracture model, PRP improves cellular proliferation and chondrogenesis during early fracture healing and increases the mechanical strength of callus during late fracture healing.^{42} The effect of PRP on fracture healing is associated with altered expression of TGF-β1 and BMP-2.^{43} Clinically, the efficacy of PRP on fracture healing has not been fully confirmed. The findings of a systemic literature search showed that there is no strong evidence supporting the routine use of PRP in either acute or delayed fracture healing.^{44} Further high-quality, randomized, and prospective clinical trials are required to determine whether PRP is beneficial in the treatment of fracture nonunions.

**Bone Marrow Aspirate**

Bone marrow aspirate has been used to enhance bone repair for more than two decades. Many clinical studies have shown its safety and efficacy in treating fracture nonunions and bone defects.^{45,46} It is well established that bone marrow contains mesenchymal stem cells, which can be expanded in culture and can differentiate into osteoblasts, chondrocytes, and other connective tissue cells in vitro under appropriate conditions. Bone marrow is also the source of circulating endothelial progenitors that can contribute to adult vasculogenesis. Therefore, some of the effects of bone marrow aspirate on fracture healing could be due to the local application of osteochondrogenic cells and/or endothelial progenitor cells during bone healing. However, there is not enough evidence showing these cells can actually differentiate into osteoblasts, chondrocytes, or endothelial cells, and further investigation is required to determine the exact role of these transplanted cells in fracture healing.

**Bone Morphogenetic Proteins**

BMPs were first discovered in 1965 by Urist; at least 20 different BMPs have been found thus far. All of these BMPs, except BMP-1, belong to the group of TGF-β superfamily growth factors. BMP-1 is a metalloprotease that acts on procollagen I, II, and III. Among all the BMPs, BMP-2 and BMP-7 have been extensively studied for their capacity to induce bone in a variety of conditions. BMPs are capable of recruiting stem cells from distant sites and inducing osteoblast and chondrocyte differentiation, leading to ectopic bone formation. Recent studies have shown that BMPs are involved in angiogenesis, the process of new blood vessel formation and vascular repair. BMP-7 is capable of inducing new blood vessel formation in chick chorioallantoic membranes,^{47} and BMP-2, which acts in a manner similar to that of BMP-7, can increase vascularization of tumors.^{48} The US Food and Drug Administration (FDA) has approved the clinical use of rhBMP-2, marketed as Infuse Bone Graft, in acute open fractures of the tibia and spinal fusion surgery, and recombinant human BMP-7 (rhBMP-7), or osteogenic protein-1 (OP-1), as an alternative to autograft in recalcitrant long bone nonunions and in compromised patients requiring revision posterolateral lumbar spinal fusion under a Humanitarian Device Exemption (HDE). Level I clinical evidence demonstrates that rhBMP-2 improves the repair of open tibia fractures.^{49} Prospective case series studies have shown that rhBMP-7 is effective in treating tibial and femoral nonunions.^{50,51}

**Vascular Endothelial Growth Factor**

Blood supply is crucial for normal fracture healing. Lack of perfusion is often associated with delayed union or nonunion. Investigators have suggested that stimulating vascular repair may represent a novel method to stimulate bone healing. Vascular repair after bone injury occurs largely through a process called angiogenesis, which is the sprouting of new blood vessels from preexisting ones. During fracture healing, angiogenesis is orchestrated by a variety of factors including VEGF, FGFs, and matrix metalloproteinases (MMPs).
Among these factors, VEGF is currently recognized as the most potent angiogenic factor, and it plays an important role during both skeletal development and adult bone regeneration.\(^{52}\) In fracture calluses, VEGF is expressed by hypertrophic chondrocytes and may be released from cartilage matrix by matrix degradation mediated by MMP-9.\(^{12}\) VEGF acts on endothelial cells and induces vascular invasion of the hypertrophic cartilage. The ability of VEGF to enhance bone regeneration has been explored in several animal models. VEGF delivered as a protein or through genetic approaches can promote healing of femoral fractures in mice,\(^{53}\) radius segmental defects in rabbits,\(^{53,54}\) and bone drilling defects in rats.\(^{55}\) VEGF and BMPs may have synergistic effects on bone regeneration.\(^{56}\) Recently, another unique approach has been developed to enhance angiogenesis during fracture healing by regulating hypoxia inducible factor-1α (HIF-1α), which is a master regulator of VEGF expression.\(^{66}\) Inhibiting HIF prolyl hydroxylase, an enzyme that deactivates HIF-1, can stabilize HIF/VEGF production, increase angiogenesis, and improve fracture healing.\(^{57}\)

**FGFs are involved in bone development and fracture healing.** The expression patterns of FGFs and their receptors during bone repair have been well documented.\(^{58}\) In animal bone repair models, both acidic FGF and basic FGF (bFGF) stimulate cartilage formation, leading to larger fracture calluses.\(^{59}\) bFGF may also increase the number of osteoclasts and accelerate remodeling of fracture calluses.\(^{60}\) The effects of bFGF on bone formation are dose dependent. There is evidence showing that bFGF stimulates osteogenesis at lower doses but inhibits bone formation at high doses.\(^{61}\) Clinical trials are required to establish the effectiveness of FGFs on fracture healing or repair of bone defects in patients.

**Parathyroid Hormone**

Parathyroid hormone (PTH) is secreted by the parathyroid glands and its normal function is to increase the calcium levels of the blood by indirectly stimulating bone resorption, increasing renal reabsorption of calcium, and increasing intestinal calcium absorption. Low-dose, intermittent administration of PTH has anabolic effects on bone metabolism, whereas continuous administration of high doses leads to catabolic effects. PTH (1-34), the 1-34 amino acid segment of recombinant human PTH, is the active form of PTH. The commercially available PTH (1-34), teriparatide, is an FDA-approved drug for postmenopausal osteoporosis and osteoporosis associated with sustained systemic glucocorticoid therapy. It can increase the bone mineral density in the lumbar spine and femoral neck in patients with osteoporosis, and reduce fracture risk.\(^{62}\) Recent experimental studies have shown that PTH (1-34) is effective for enhancing fracture healing in animals.\(^{63}\) PTH (1-34) treatment stimulates early bone and cartilage formation, increases callus formation, accelerates callus remodeling, and improves the biomechanical properties of callus tissue. Further mechanistic analyses show that systemic administration of PTH (1-34) up-regulates the expression of Osx and Runx2 in bone marrow–derived mesenchymal stem cells and promotes osteoblast differentiation.\(^{64}\) These data suggest that PTH (1-34) is a promising treatment of fracture non-union. However, to date there is no published clinical study on the efficacy of PTH (1-34) on fracture healing.

**Wnt**

Wnts are a family of extracellular cell–cell signaling molecules that regulate embryogenesis and tissue homeostasis in adults. It has been recently documented that Wnt signaling plays an important role in fracture healing. In the adult skeleton, Wnt signaling proteins are expressed by osteocytes, in the endosteum and bone marrow.\(^{65}\) After bone injury, Wnt signaling is upregulated and inhibition of the Wnt pathway leads to a delay in bone regeneration.\(^{65,66}\) Mutations of a Wnt coreceptor, Lrp5, result in constitutive Wnt activation. In mice that lack Lrp5, proliferation of skeletal progenitor cells at the site of bone injury is increased, but bone repair is delayed.\(^{65}\) Further research has shown that Wnt signaling inhibits undifferentiated mesenchymal cells but may have positive effects on cells that have committed to the osteoblast lineage.\(^{66}\) These research findings suggest that the Wnt signaling pathway is a potential target to enhance fracture healing. Indeed, lithium treatment, which activates the Wnt pathway, is found to accelerate bone formation and increase bone mass in mice.\(^{67}\) However, lithium treatment should be avoided during the early stage of fracture healing because activated Wnt signaling has a negative effect on undifferentiated mesenchymal cells.\(^{68}\)

**Ultrasound/Electrical Stimulation**

Biophysical treatments such as electrical stimulation, ultrasound, extracorporeal shock wave therapy (ESWT), and vibration can improve fracture healing. Electrical stimuli create low levels of electric currents in tissue, leading to lowered tissue Po2, increased expression of factors such as TGF-β and BMPs, improved neovascularization, and enhanced osteogenesis. Four methods have been developed to deliver electric stimuli to the fracture site: direct current, capacitively coupled electric fields, pulsed electromagnetic fields, and combined magnetic fields.\(^{69}\) These methods have been promoted as useful treatments of established nonunions and failed spinal fusion. Low-intensity pulsed ultrasound (LIPUS), as a physical method to enhance bone repair, has gained popularity recently. The exact mechanisms through which LIPUS improves fracture healing have not been well determined but could include altered gene expression, increased blood supply, and the creation of a gradient of mechanical strain. Both experimental and clinical studies have shown that LIPUS is effective in treating delayed union and nonunions, achieving healing rates at about 80%. It appears that LIPUS may work better on delayed fracture healing.
than nonunions and is also effective on septic fracture nonunions.\textsuperscript{70} There are reports showing that ESWT can be used to treat delayed fracture healing and nonunions, however, its efficacy needs to be better determined. Currently, ESWT is still considered an experimental clinical procedure.\textsuperscript{71} Additionally, providing cyclic mechanical loadings to the fracture site using low-magnitude high-frequency vibration may also stimulate bone formation.\textsuperscript{72}

### Summary

Major advancements have been achieved in the field of bone repair during the last several decades. Further discoveries in stem cell biology, molecular biology, biomaterials, and tissue engineering will continue to improve understanding of cellular and molecular factors. It is expected that orthopaedic surgeons will have more options available to stimulate and enhance bone repair.

### Annotated References


Nicotine affects cultured osteoblast cells in a biphasic
1. Principles of Orthopaedics

manner. High levels of nicotine inhibit cell proliferation and downregulate gene expression of osteoclastin, type I collagen, and alkaline phosphatase. Low levels of nicotine have opposite effects.


In a mouse fracture model, diabetes increases chondrocyte apoptosis and osteoclastogenesis, leading to cartilage loss and less callus formation. These effects of diabetes can be reversed by insulin.


The authors reviewed the current evidence for an association between HIV infection and poor fracture healing.


Bisphosphonate use is associated with longer times to radiographic union of distal radius fractures. However, the differences in healing times are small and not considered clinically significant. The authors concluded that bisphosphonate therapy can be continued after fracture. Level of evidence: III.


In a cohort of older adults with humerus fractures, bisphosphonate use was associated with an approximate doubling of the risk of nonunion. Clinical evidence level III.


In this matched case-control study, the authors found that “prolonged bisphosphonate use is associated with low-energy subtrochanteric/shaft fractures in postmenopausal women who have no obvious secondary causes of bone loss. Furthermore, bisphosphonate use of greater than 5 years was associated with a characteristic fracture of the femur, defined as a simple transverse or oblique fracture with cortical thickening and beaking of the cortex in the subtrochanteric/shaft region. This fracture is an atypical fracture for osteoporotic women.” Level of evidence: III.


In this study, the authors analyzed low-energy subtrochanteric insufficiency fractures in 17 patients who have been on alendronate therapy for an average of 4.8 years. The authors identified a characteristic fracture configuration suggestive of an insufficiency stress fracture. This consisted of (1) cortical thickening in the lateral side of the subtrochanteric region, (2) a transverse fracture, and (3) a medial cortical spike. In addition, 9 (53%) patients had bilateral findings of stress reactions or fractures. Level of evidence: III.


The authors reviewed 284 records for hip or femur fractures among 14,195 women in three large, randomized bisphosphonate trials: the Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial, and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT). The authors concluded that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare, even among women who had been treated with bisphosphonates for as long as 10 years. There was no significant increase in risk associated with bisphosphonate use, but the study was underpowered for definitive conclusions. Level of evidence: I.


Rats with tibia fractures that were treated with parecoxib or indomethacin for 7 days after injury exhibited decreased bone mineral density and biomechanical properties of fracture callus for 2 to 3 weeks.


This article reviews the effects of gamma irradiation on the biologic and mechanical properties of allograft bone.


The authors present a critical overview of the current clinical applications of DBM.


The authors enrolled 120 acute, closed, unstable tibial plateau fractures. Subarticular defects were filled with either calcium phosphate cement or autogenous bone graft. The cement did not improve the union rates and the time to union. However, the bioresorbable calcium phosphate cement used in this study appears to be a better choice, at least in terms of the prevention of subsidence, than autogenous iliac bone graft for the treatment of subarticular defects associated with unstable tibial plateau fractures. Level of evidence: I.


The authors prospectively randomized 47 patients with 52 closed displaced intra-articular calcaneal fractures necessitating operative fixation to receive ORIF alone (n = 28) or ORIF plus alpha-BSM (n = 24). The results confirmed the safety of alpha-BSM and the alpha-BSM treated fractures better retained Böhler’s angle at 6 months and 1 year after surgery. Level of evidence: I.


In a rat femur fracture model, PRP enhances bone formation, which is associated with changes of TGF-ß1 and BMP-2 expression.


This systemic literature review found limited clinical studies and no solid evidence for the efficacy of PRP in acute or delayed fracture healing.


The authors treated 68 patients with tibial nonunion with BMP-7. Nonunion healing was verified in 61 patients (89.7%) in a median period of 6.5 months. Level of evidence: III.

Section 1: Principles of Orthopaedics

(suppl 3):S54-S61.

The authors treated 30 femoral nonunions with BMP-7. Nonunion healing was verified in 26 of 30 cases in a median period of 6 months. Level of evidence: III.


Implanted ectopically, VEGF increases tissue vascularity and BMP-2 induces bone formation in rats. A combination of VEGF and BMP-2 significantly enhances ectopic bone formation compared to BMP-2 alone.


The authors quantitatively evaluated the temporal expression patterns of FGFs and their receptors up to 14 days after fracture in a mouse model.


In a sheep bone defect model, the addition of 200 mg of bFGF to tricalcium phosphate (TCP) cement decreased bone ingrowth into the cement.


This paper summarizes the experimental evidence that suggests PTH (1-34) accelerates callus formation and remodeling, and improves the biomechanical properties of the fracture callus.


In a mouse model, teriparatide treatment increases osteocalcin expression and improves fracture healing. Bone marrow–derived mesenchymal stem cells isolated from teriparatide-treated mice exhibit accelerated osteoblast maturation.


The authors found that Wnt signaling is activated during fracture healing. Inhibition of Wnt signaling prevents the differentiation of osteogenic progenitor cells and reduces bone regeneration.


Beta-catenin signaling is regulated by Wnt ligands. Absence of β-catenin inhibits fracture healing and activation enhances bone repair.


This comprehensive paper reviews the role of Wnt pathway in bone regeneration.


70. Romano CL, Romano D, Logoluso N: Low-intensity

This article summarizes the effects of LIPUS on fracture healing, including an updated review of the basic science, animal studies, and clinical trials of LIPUS.


In a rat model, low-magnitude high-frequency vibration improves fracture healing through increased callus formation and accelerated remodeling.