ABSTRACT
Orthopedic trauma care and fracture management have advanced significantly over the last 50 years. New developments in the biology and biomechanics of the musculoskeletal system, fixation devices, and soft tissue management have greatly influenced our ability to care for musculoskeletal injuries. Many therapies and treatment modalities have the potential to transform future orthopedic treatment by decreasing invasive procedures and providing shorter healing times. Promising results in experimental models have led to an increase in clinical application of these therapies in human subjects. However, for many modalities, precise clinical indications, timing, dosage, and mode of action still need to be clearly defined. In order to further develop fracture management strategies, predict outcomes and improve clinical application of newer technologies, further research studies are needed. Together with evolving new therapies, the strategies to improve fracture care should focus on cost effectiveness. This is a great opportunity for the global orthopedic community, in association with other stakeholders, to address the many barriers to the delivery of safe, timely, and effective care for patients with musculoskeletal injuries in developing countries.

Key words: Trauma, fracture, bone stimulation therapies, orthopedic community

INTRODUCTION
The global burden of injury is staggering, and injuries are predicted to be a leading cause of death and disability over the next few decades. In 2001, injuries in developing countries accounted for 11% of the world’s disease burden, and ranked 11th in all causes for both mortality and morbidity. It is also estimated that in the developing countries 6 million will die and 60 million will be injured, or disabled, in the next 10 years. With fractures accounting for the majority of trauma in developing nations, novel therapies are desperately needed to optimize patient outcomes.

Orthopedic trauma care and fracture management have seen significant advances over the last 50 years. New developments in the biology and biomechanics of the musculoskeletal system, fixation devices, and soft tissue management have greatly influenced our ability to care for musculoskeletal injuries. Many therapies and treatment modalities have the potential to transform future orthopedic treatment by decreasing invasive procedures and providing shorter healing times. In order to further develop fracture management strategies, predict outcomes, and improve clinical application of newer technologies, further research studies are needed. Together with evolving new therapies, the strategies to improve fracture care should focus on cost effectiveness. This is a great opportunity for the global orthopedic community, in association with other stakeholders, to address the many barriers to the delivery of safe, timely, and effective care for patients with musculoskeletal injuries in developing countries.

FRACTURE OUTCOMES: CURRENT CHALLENGES
The biology of fracture healing is an organized and complex process that restores skeletal integrity by reconstitution of bone. Although fracture healing is a consistent and reliable biological response, its failure can lead to devastating clinical consequences. It is estimated that delayed or impaired healing will occur in 5–10% of the 5.6 million fractures that occur annually in the United States, and up to 10% of all fractures will require additional surgical procedures for impaired healing. Furthermore, a recent literature from the United States suggests that the lifetime risk of fracture is 50% for males and 33% for females.

The standard treatment in developed countries for delayed healing and nonunions has been open surgical fixation with autogenous bone grafting. This method provides the essential elements for bone regeneration: osteoinduction, osteoconduction, and osteoprogenitor cells. However, a frequent problem associated with autogenous bone grafting is donor site morbidity. Currently, many other biological and biophysical approaches are available to minimize the
occurrence of delayed unions and nonunions. The biological approaches include gene therapy, tissue engineering, osteoconductive biomaterials, growth factors, bone-marrow aspirates, and osteocompetent cells. Mechanical stimulation by low-intensity ultrasound, electromagnetic fields, and extracorporeal shock-wave therapy are some of the biophysical approaches available. Recent studies have also looked at the impact of drugs and hormonal therapy, especially parathyroid hormone, on bone repair.13

**BIOLICAL METHODS TO FACILITATE BONE HEALING AND REPAIR**

Induction of bone healing by chemical, biophysical, and hormonal means is a rapidly growing area. Osteoconductive materials act as a scaffold and support new bone formation through in-growth of the host bone.14-17 There are several types of osteoconductive agents that can be used to heal fractures. Calcium sulfates and phosphates are strong in compression but weak in tension and shear.18,19 Hydroxyapatite and tricalcium phosphate are examples of calcium phosphates with osteoconductive and osteointegrative properties.16,17 Calcium sulfate has predictable resorption in vivo due to minimal trace elements and biodegradability whereas tricalcium phosphate is more rapidly absorbed than hydroxyapatite due to increased porosity and solubility.14 Due to these properties, tricalcium phosphate is inadequate when structural support is required. Type I collagen is another osteoconductive material and is the most abundant extracellular bone-matrix protein. Type I collagen by itself is a poor graft substitute but when combined with bone morphogenetic proteins, osteoprogenitor precursors or hydroxyapatite, its osteoconductive potential increases considerably.17 Bioactive glass, biodegradable polymers, and porous and plasma-coated metals are other examples of osteoconductive materials, but all of these materials need further studies to analyze their clinical effectiveness.16

Several randomized studies of osteoconductive materials have shown promising results. Shors compared coralline hydroxyapatite to an autograft for 174 long-bone defects and found that time to union was not significantly different at 4.5 months.19 Buchholz et al. in an earlier study of coralline hydroxyapatite in tibial plateau fractures reported similar results.20 Mattsson and Larsson compared closed reduction and cannulated screw fixation versus cannulated screws plus calcium phosphate cement in the treatment of displaced fractures of the femoral neck and found no difference in pain and muscle strength between groups, but 34 patients (14 in the control group and 20 in the calcium phosphate group) required conversion to total hip replacement.21 Mattsson et al. also reported favorable outcomes with the use of calcium phosphate cement in unstable peritrochanteric fractures of the neck of femur.22-25 Several authors have reported favorable results with the use of calcium phosphate cement.26,27 Chapman et al. compared the use of iliac bone graft to a collagen composite for long-bone fractures and found no difference in outcomes except for a higher rate of infection with the use of iliac bone graft.28 Cornell et al. reported similar results and found no significant difference in hospital length of stay or pain scores.29

Various cell types, growth receptors, and growth factors are present within a fracture callus and modulation of these growth factors is postulated to positively influence bone healing.30-33 Research efforts have focused on the development of appropriate carriers or delivery systems for growth factors in order to effectively deliver them to the fracture site. Type I collagen, synthetic polymers and hyaluronic acid gels are examples of such agents.34-37 Unlike bone morphogenetic proteins (BMPs) which are proven in several human clinical trials as a potent osteoconductive material, certain other growth factors, such as transforming growth factor-beta, insulin-like growth factor, and platelet-derived growth factor-beta, have insufficient preclinical data to determine efficacy.38-52 Friedlaender et al. reported that using recombinant human morphogenetic protein-7 (rhBMP-7) was as good as bone grafting and was not associated with donor site morbidity that usually occurs in more than 20% of patients receiving an autograft.53 The BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group compared the effects of two different exogenous rhBMP-2 concentrations versus no rhBMP-2 on the healing of nailed open tibial fractures.47 This group reported a dose-dependent effect, with faster healing times and fewer secondary interventions for delayed unions and nonunions. Several Level-I studies of rhBMPs have shown promising results as well.48,52 Further studies are needed to determine appropriate dosages, optimum time, and modes of delivery, duration of treatment, and precise clinical indications for use. It is also important to determine a cost-to-benefit analysis for the use of these agents.

Several studies have looked at the role of percutaneous bone-marrow aspirates in the closed treatment of fractures, although, currently no Level-I study has directly compared the efficacy of bone-marrow aspirates to autologous bone graft. Although little information is available regarding the number and concentration of cells that are necessary for bone repair, several studies have reported on the human variability with respect to bone-marrow cellularity and osteoblast progenitor-cell prevalence.54-59 Further randomized studies examining the growth factor use and its combination with collagen to increase stem-cell proliferation and differentiation are needed.60

Deminerlized bone matrix is an osteoconductive agent that...
provides no structural support but is used for filling defects and cavities. They are produced by acid extraction of bone and contain noncollagenous proteins, growth factors, BMPs and type I collagen. Demineralized bone matrix is available in various formulations: freeze-dried powder, granules, strips, gel, chips, or calcium sulphate granules. The efficacy of these products ranges widely, depending on bone type, sterilization process, carrier, quantity of BMPs present, and ratios of each. The osteoinductive efficacy of demineralized bone matrix has been determined in animal studies but, currently no randomized studies have been done on humans comparing the effects of demineralized bone matrix with that of the autologous bone graft. The current recommendation for the use of demineralized bone matrix is as graft extenders.

Platelet gels have generated a considerable interest in the recent years. These are made by isolating a concentration of platelets from the patient’s own blood. Platelet gels contain growth factors and function as osteoinductive agents. They can thus play a key role in bone formation and maturation of osseous fusions. Current indications for the use of platelet gels are as graft extenders. Further studies are needed to assess the optimum concentration of the different factors and to determine which factors would provide the greatest effect.

Human gene therapy for fracture repair is another attractive option due to the decreased invasiveness of the technique. However, presently there are no Level-I studies to inform clinical decision making regarding bone repair. This therapy relies on treating human diseases by transferring genetic material to individual cells, thus re-establishing damaged cellular function, introducing a new function, and/or interfering with an existing function. Three fundamental steps critical for the success of gene therapy are identification of the specific genetic material to be transferred, the method of transfer, and the cell type that would incorporate the material. Encouraging preclinical data are available on tissue repair, cancer, and regeneration of bone cartilage, ligament, tendon, meniscus, and intervertebral disk. This technique has also been applied to other areas including osteoporosis, aseptic loosening, genetic diseases, musculoskeletal infections, and tumors. Spinal fusions and repair of segmental defects of long bones have seen impressive preclinical study results.

Orthopedic tissue engineering is still in experimental stages and combines the use of three-dimensional scaffold materials, cells, and release of growth factors. The goal in tissue engineering is reconstitution of tissues that have failed to regenerate or heal spontaneously. Pleuripotent mesenchymal stem cells are capable of differentiating into bone-forming osteoblasts with appropriate growth factors present both in vitro and in vivo. These cells are biopsied from the patient and are grown on engineered biomaterials in vitro and implanted at the desired treatment location. Many novel substances like biodegradable polymers and ceramics with adsorbed growth factors are in trial as substitutes for skeletal elements such as cartilage and bones.

Intermittent exposure to parathyroid hormone may benefit fracture healing and implant fixation, as seen in preclinical studies. Continuous exposure to parathyroid hormone results in bone resorption, but intermittent doses result in bone formation through an increased osteoblastic activity. Further clinical studies are needed to determine if this hormone will benefit patients with fractures, what the optimal treatment duration might be, and if resorption inhibitor therapy after parathyroid hormone treatment will improve fracture healing.

**Conclusions**

Musculoskeletal injuries are a substantial burden in developing countries such as India; the problem is complex, multidimensional, and can only be solved through a multidisciplinary, multisectoral effort. While recognizing the importance of prevention, improving treatment is essential. Many therapies and treatment modalities have the potential to transform future orthopedic treatment by decreasing invasive procedures and providing shorter healing times. In order to further develop fracture management strategies, predict outcomes, and improve clinical application of newer technologies, further research studies are needed.

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