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Bone fracture healing in mechanobiological modeling: A review of principles and methods

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ABSTRACT

Bone fracture is a very common body injury. The healing process is physiologically complex, involving both biological and mechanical aspects. Following a fracture, cell migration, cell/tissue differentiation, tissue synthesis, and cytokine and growth factor release occur, regulated by the mechanical environment. Over the past decade, bone healing simulation and modeling has been employed to understand its details and mechanisms, to investigate specific clinical questions, and to design healing strategies. The goal of this effort is to review the history and the most recent work in bone healing simulations with an emphasis on both biological and mechanical properties. Therefore, we provide a brief review of the biology of bone fracture repair, followed by an outline of the key growth factors and mechanical factors influencing it. We then compare different methodologies of bone healing simulation, including conceptual modeling (qualitative modeling of bone healing to understand the general mechanisms), biological modeling (considering only the biological factors and processes), and mechanobiological modeling (considering both biological aspects and mechanical environment). Finally we evaluate different components and clinical applications of bone healing simulation such as mechanical stimuli, phases of bone healing, and angiogenesis.

Contents

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1. Introduction

Bone fracture is one of the more common injuries, and is associated with treatment costs exceeding billions of dollars, societal productivity loss, and individual disability (Pivonka and Dunstan, 2012; Bonafede et al., 2013). As access to motorized transportation has increased throughout the developing world, there has been a dramatic increase in trauma and life-threatening long bone fractures (Web-based Injury Statistics Query and Reporting System (WISQARS); Cottrell and O'Connor, 2010). Fracture healing is an intricate coordination of various cellular and mechanosensitive processes. Approximately five to 10% of fractured bones end in nonunion and/or incomplete healing (Einhorn, 1995; Praemer et al., 1992). Understanding the biomechanical aspects of the healing process in detail is a crucial for orthopedic surgeons to properly create the optimal healing environment for an injured bone (Pivonka and Dunstan, 2012; Einhorn and Gerstenfeld, 2015).

There are two general approaches to studying the bone healing process: 1) experimental methods and 2) computational modeling. Both of these methods have benefits and limitations. Experimental methods work with real scenarios and generally provide results attributable to clinical applications. However, experimental methods require state of the art equipment, high accuracy, controlled conditions, high cost, and are often confounded by other factors such as unknown subject backgrounds, comorbidities, and genetic variation (Lacroix et al., 2002; Moran et al., 2016). On the other hand, computational modeling and simulation of the bone healing process have been utilized to overcome the limitations associated with experimental methods (Lacroix and Prendergast, 2002). Nevertheless, computational modeling approaches have their own limitations in clinical applications. Thus, these models need to be further developed and validated in order to achieve clinically relevant results (Pivonka and Dunstan, 2012; Carlier et al., 2015a). These models help us better understand the mechanism of bone healing by emphasizing the known correlation between the mechanical environment and the bone healing process (Claes and Heigele, 1999; Prendergast et al., 1997). They can even help us predict how mechanical environments and drug treatment strategies affect the biological processes and cellular activities of bone healing (Geris et al., 2010a; Carlier et al., 2014). Modeling can also provide valuable insight for the design, optimization, and final outcome predictions in future treatment strategies. Nevertheless, computational modeling approaches have their own limitations in clinical applications. Thus, these models need to be further developed and validated in order to achieve clinically relevant results (Pivonka and Dunstan, 2012; Isaksson, 2012).

This review aims to summarize the present understanding of the biomechanical processes affecting healing and nonunion. We first review the bone healing biology, factors, and processes previously addressed in modeling approaches. Some of the well-known mechanobiological regulation theories are then reviewed, and specific mechanical factors which influence biological processes and cellular activities of bone healing are outlined. Finally, we focus on the mechanobiological model's potential contributions to different real-world clinical and research applications, followed by prospective research directions.

2. Biology of Bone Healing

Fracture healing starts with an initial anabolic phase, where local tissue volume increases through inflammation. Following bone fracture, a hematoma is formed at the fracture site, which acts as a temporary scaffold for stem cell differentiation into fibrous tissue, cartilage, and bone. In the inflammatory phase, several biological factors including TNF-Alpha, transforming growth factor-beta (TFG-β) superfamily, bone morphogenetic proteins (BMP), IL-1β, IL-6, IL-17F, and IL-23 are released. In addition to these cytokinetic factors, mechanical loads such as strain or hydrostatic pressure also play a vital role in bone fracture healing (Pivonka and Dunstan, 2012; Einhorn and Gerstenfeld, 2015; Claes et al., 2012; McKibbin, 1978).

The aforementioned biological factors and the mechanical environment regulate the activities of mesenchymal stem cells (MSC), which are some of the most important contributors to the bone formation (Nagel and Kelly, 2010), in addition to the activities of chondrocytes, osteoblasts, fibroblasts, and endothelial cells (Prendergast et al., 1997; McKibbin, 1978; Pauwels, 1959). However, the interaction between cellular activities and the mechanical environment remains undefined (Pivonka and Dunstan, 2012; Einhorn and Gerstenfeld, 2015).

With progressive healing, cartilaginous callus (soft callus) is formed through the activities of skeletal and endothelial cells, which bridge the gap between the bone fragments (Pivonka and Dunstan, 2012; Einhorn and Gerstenfeld, 2015; Claes et al., 2012). Soft callus then progresses to hard callus. There are two typical mechanisms of bone formation: intramembranous ossification and endochondral ossification. In intramembranous ossification, MSCs differentiate to osteoblasts, creating bone tissue directly in an anabolic process (typical of flat bones such as skull and clavicle). In endochondral ossification, MSCs differentiate into chondrocytes, which create cartilage tissue. The synthesized cartilage extracellular matrix (ECM) mineralizes through chondrocyte apoptosis. Subsequently, the osteoblast cells penetrate this dead structure and lay down the bone tissue (Einhorn and Gerstenfeld, 2015; McKibbin, 1978; Oryan et al., 2015). Long bones typically grow and heal by this process.

There are two forms of bone healing: primary and secondary. Primary bone healing occurs when the bony fragments are tightly fixed together under compression from implantation. There is no callus formation, and two bone fragments are connected together and healed directly by osteoclasts and osteoblasts activities (Claes et al., 2012; Marsell and Einhorn, 2011). Secondary bone healing, the most common form of bone healing, occurs when there is a small amount of motion in the fracture site. The interfragmentary motion causes soft callus formation, and leads to secondary bone formation through both intramembranous and endochondral ossifications (Claes et al., 2012; Gerstenfeld et al., 2006). This form of bone healing begins with the anabolic phase, and overlaps with the catabolic phase when callus volume is reduced. Following these processes, the bone remodeling phase begins by coordinated osteoblast and osteoclast activities over a span of several months. Callus tissues are reabsorbed and lamellar bone is formed (Schindeler et al., 2008; Little et al., 2007). Fig. 1 illustrates a clinical example of this healing and remodeling process in a comminuted spiral humerus shaft fracture over a two-year time period.

Fig. 1 illustrates a typical humeral shaft fracture that is clinically recognized as not requiring surgery for its successful healing. Humeral extra-articular fractures, even very distal ones, can be treated successfully without surgical fixation simply with a brace and the bone's ability to self-heal through callus formation when mechanically stable. The array of instrumentation and techniques at an orthopedic surgeon's disposal provides the means to create the most ideal and stable healing