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Principles of bone formation driven by biophysical forces in craniofacial surgery

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Abstract

Biophysical forces, particularly mechanical loading and electromagnetic signals, are important regulators of bone formation. Indeed, the regenerative capacity of bony tissue is largely the result of the bone's capacity to recognise the functional environment required for the emergence and maintenance of a structurally intact bone. Biophysical methods of stimulation have therefore been introduced and have proved successful in clinical practice with craniofacial bones. Distraction osteogenesis, application of ultrasound, calculated transfer of stresses, and exposure to an electromagnetic field are some examples of biophysically driven approaches to influencing bone formation. The purpose of this review is to provide an insight into cellular and tissue models that are used to study the effects of biophysical stimuli on bone.

Keywords: Bone; Biophysical strategies; Mechanobiology

Introduction

Bone is a complex, highly organised tissue. It comprises a structured extracellular matrix composed of inorganic and organic elements that contains a number of types of cell that are responsible for its metabolism and upkeep and are responsive to various signals.[1] The formation of bone is a multistep process that is characterised by interactions between the various cells of bony tissue, components of the extracellular matrix, and inorganic minerals.[2] As bone has to be structurally adapted to various functions, the activity of cells and the subsequent reaction in the tissue varies with the type, the anatomical site, and the loading conditions.[3] Craniofacial bones are specialised structures in which muscles, joints, and teeth are adapted to operate in a complex synergy within the highly developed masticatory system. Biomechanical transfer of load is a key effector in most craniofacial bones, so it has an important role in humans because load-related deformation of tissue can both increase bone formation and decrease bone resorption.[4] Indeed, the absence of load can lead to lower production of bone-matrix protein and loss of mineral content, as occurs in the lower limbs of astronauts who have long flights in space. Loading leads to a complex sequence of biophysical events. Deformation of cells in the microenvironment of the tissue and fluid-flow-related generation of electrical potentials are the main consequences of loading in bone.[5]

When mechanical or electrical stimuli are applied therapeutically to improve the formation of bone, one has to be aware that they exert their effects within the various structures of the skeleton. The influence of physical factors in skeletal regeneration can generally be considered at organ, tissue, cellular, and molecular levels. Understanding the overall process of biophysical signalling requires an appreciation of these various branches of study and knowledge of how one process relates to and influences the next. Firstly, biophysical stimuli can be analysed for their effect on whole bones. Secondly, the effects on multicellular systems can be evaluated by examining the reaction of tissue to the biophysical

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microenvironment. Thirdly, cellular and molecular reactions can be detected by measuring effects at microscale level.

Biophysical stimuli exert their effects in humans at distinct skeletal sites. The relation between the stimulus that is applied clinically and the outcome in terms of histological and clinical success is complex. Physical stimuli are altered by the structure of the site where the stimulus is applied. The transfer of load through adjacent structures (joints, ligaments, and muscles) and the absorption of load by exposure to an electrical field have an important bearing on the resultant biophysical signal at the desired effector site. Both patient-specific and technique-specific factors play an important part. The specific forms of therapeutic biophysical stimulation and the effect of dose and timing of the application must be calculated and validated carefully at the different types of bony tissue. Key requirements of using biophysical forces are therefore to define the precise cellular response to the stimulation signal in an in vitro environment and to use well-established animal and clinical models to quantify and optimise the type of therapeutic stimulation. This seems to be achievable through collaboration among different disciplines, using defined scientific methods.

Organ level

Some skeletal characteristics have to be taken into account when considering biophysical effects on bones. The main purpose of bone is to provide structural strength commensurate with its mechanical use. This means that bones provide enough strength to prevent normal physical loads from damaging the integrity of the tissue. Recent research has indicated that bones can adapt amazingly well to a changing functional environment; this is often referred to as phenotype plasticity.[6] Specific biophysical signals are assumed to be largely responsible for controlling this adaptive mode of modelling of bony tissue. When loads act on whole bones, the tissue begins to deform, causing local strains (typically reported in units of microstrain; 10,000 microstrain = 1% change in length). Various investigators have shown that reactive loads give rise to strains at fundamental frequencies ranging from 1 to 10 Hz. Peak magnitudes of strain measured in various species were found to have a remarkable similarity, ranging from 2000 to 3500 microstrain with no great difference between long bones and craniofacial bones. Lanyon et al.[7] showed that within a single period of loading, the remodelling process was saturated after only a few (<50) loading cycles. Repeated applications of load then produced no extra effect. Frost offered a unique theory to explain the load-related modelling and remodelling processes in bone.[6] He showed that the adaptive mechanisms included basic multicellular units. Effector cells within these units function in an interdependent manner. While hormones may bring about as much as 10% of the postnatal changes in bone strength and mass, 40% are established by mechanical factors. This effect, reflected in the loss of more than 40% of bone mass in the lower limbs of patients with paraplegia, stresses the effect of biophysical signals on bone modelling and remodelling.[5]

The functional biological environment of any bony tissue is thus derived from a dynamic interaction between various active basic multicellular units exposed to a biophysical microenvironment that undergoes continuous load-related changes. Formation of bone occurs through drifts of formation and resorption to reshape, thicken, and strengthen a bone or trabecula by moving its surfaces around in tissue space. Remodelling of bone also involves both resorption and formation. Basic multicellular units turn bone over in small packets through a process in which an activating event causes some resorption followed by formation. This basic multicellular unit-based remodelling operates in two modes: "conservation mode" and "disuse mode". Specific ranges of threshold of strain seem to control which of these two modes is active at any given time. While the strain-related bone-modelling theory was long assumed to be applicable only to intact bones, recent research has shown that this adaptive behaviour is also present in the healing processes in bone.

Tissue level

It is important to recognise that mechanical and electrical effects are exerted simultaneously in bone.[8] Complex mechanical and electrical interactions during the modelling and remodelling processes integrate the action of several signals to form the final response. Deformation of tissue is a key stimulus in bone physiology and leads to a complex non-uniform biophysical environment within bony tissue, consisting of fluid flow, direct mechanical strain, and electrokinetic effects on bone cells. At the tissue level, some researchers assumed that the differentiating tissue was a continuous material and evaluated biophysical signals by characterising the stimulus in terms of mechanical engineering quantities, such as stress and strain. Based on the material properties of tissue and approximations of tissue loading in the different experimental and clinical conditions, these quantities were calculated throughout the tissue and were related to various patterns of differentiation in the tissue. The biophysical mechanisms underlying the tissue response were directly related to mechanical effects, electromechanical effects, or increase in molecular transport mechanisms.[8] Pressure, distortion, pressure gradients, and dissipation of energy are additional mechanical quantities at tissue level that were measured and related to tissue responses by other authors.[5]

Load-induced flow of interstitial fluid may provide a convergence feature between electrical and mechanical signals and so trigger the formation of hard tissue in adaptation.[9] Loading of bone leads to a deformation of cells in the microenvironment of the tissue and also to a fluid-flow-related generation of electrical potentials that exert effects on adjacent cells. Pressure gradients from mechanical loading of bony tissue elongate cells and the mineralised matrix and move extracellular fluid radially outward. Electric fields