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Review article

Low-magnitude mechanical signals and the spine: A review of current and future applications

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ABSTRACT

Animal and human studies demonstrate the anabolic properties of low-magnitude mechanical stimulation (LMMS) in its ability to improve bone formation by enhancing the proliferation of mesenchymal stem cells and their subsequent commitment down an osteoblastic lineage. Response to mechanical strains as low as 10 με have been seen, illustrating the sensitivity of mechanosensory cells to mechanotransduction pathways. Applications to the spine include treatment of osteoporosis in preparation for instrumented fusion, fracture reduction in spinal cord injury patients to slow bone mineral density loss, and bone tissue engineering and enhancement of bone-implant osseointegration for pseudarthrosis and hardware failure. This review provides an overview of the fundamentals of LMMS, highlights the cellular basis and biomechanics of how mechanical strain is translated into bone formation, and then discusses current and potential applications of these concepts to spinal disorders. Mechanical signals represent a key regulatory mechanism in the maintenance and formation of bone. Developing practical clinical applications of these mechanotransduction pathways continues to be an important area of investigation in its relation to spinal pathology.

1. Introduction

Mechanical signals have long been known to serve an integral part in the formation and regulation of bone. These signals are perceived at the cellular and molecular level through mechanosensory and mechanoresponsive mechanisms as a way of detecting the overall functional loading of the skeleton. Adaptation to these physical signals then allows for the continued remodeling and maintenance of musculoskeletal tissue as a response to the external environment. German anatomist and surgeon Julius Wolff proposed in the 19th century that the shape of bone is intimately related to this mechanical stress. Modern interpretations of "Wolff's Law" have expanded upon this to describe how bone mass and architecture are regulated by biologically adaptive mechanisms that are sensitive to mechanotransduction pathways [1–3].

The use of high frequency, low-magnitude mechanical signals (LMMS) is a particular subset of mechanical stimulation that aims to replace the regulatory mechanical signals that decay over time as a function of aging or disuse [4,5]. While mechanotransduction has been well-appreciated in the general orthopedic and osteoporotic literature, its application to the spine has yet to be firmly established. Our goal is to highlight the usefulness of these principles in relation to spinal pathology. In this article, we aim to provide an overview of the fundamentals of these key mechanical signals, review the cellular basis and biomechanics of how mechanical strain is translated into bone formation, and then discuss current and potential applications of these concepts to spinal disorders.

2. Cellular basis

While the osteoblast and terminally differentiated osteocyte are widely regarded as the primary mechanosensory cells within bone, progenitor MSCs have been shown to be sensitive and responsive to mechanical signals. This mechanical stimulation has been shown to enhance the commitment of MSCs towards the osteoblastic lineage and stimulate MSC proliferation [4,6]. At the same time, there is a reduction in osteoclast and adipocyte formation [7,8]. This highlights the mechanism by which the MSC stem cell population commits itself to de novo bone formation in response to a physical stimulus by the external environment.

Mechanical loading is registered in bone as strain, which is a small deformation throughout the calcified matrix. This cell

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deformation subsequently activates further downstream mechanotransduction pathways and is the basis of how external mechanical force is translated into a signal that is recognized by cells integral to bone metabolism [9]. Detection of the mechanical environment by osteocytes is also facilitated by shear stress from load-induced fluid flow. Loading of bone pressurizes the interstitional fluid in the lacuno-canalicular network which is then driven to flow through the thin layer of non-mineralized pericellular matrix around osteocytes [10]. This flow of interstitional fluid generates a shear stress on the cell membranes of osteocytes, subsequently initiating an intracellular response to the original mechanical load [1,11].

The cellular response due to electrical potential differences has also been noted in the longitudinal and lateral axes of bone [2,3]. These mechanical strain-generated potentials are thought to be due to several mechanisms. One potential mechanism is via streaming potentials, which are electric fields created through stress-generated fluid flow. The interstitial fluid which is forced through the channels in bone contains a surplus of cations that results in voltage which is positive in the direction of flow [1]. The streaming potential by this load-induced interstitial fluid flow is able to activate several voltage-sensitive channels in the cellular membrane of osteocytes, triggering mechanotransduction pathways [12,13]. A second mechanism is through the observation that bone tissue exhibits some piezoelectric properties, by way of accumulating charge in response to an applied mechanical stress [14]. Recent studies have explored the possibility of the piezoelectric effects of collagen to influence streaming potentials as well as the steady state fluid content in bone [1,3].

The ability of cells to sense mechanical signals from the environment requires that their mechanoreceptors be in direct contact with the deformation of the extracellular space or that they distinguish changes in physical intermediaries such as local pressure or fluid shear on the plasma membrane. The candidate mechanotransduction receptors themselves are beyond the scope of this paper, but are presented and reviewed in excellent fashion by Thompson et al. [6]. The mechanotransduction pathways themselves may involve integrins, cadherins, connexins, stretch-activated ion channels, or cytoskeletal and plasma membrane components that sense changes in cell deformation [6,15].

3. Biomechanics

The quantification of normal human bone strain is an important step in understanding the response of bone to mechanical stimuli [16]. Hert et al. was one of the first groups to explore this concept by applying loads through transcutaneous pins and Bowden cables to rabbit tibiae diaphyses [17,18]. They showed in their experiments that dynamic but not static strains increased bone formation. The formation of bone then requires dynamic mechanical loading, such that there is a variable timing frequency between loads [19,20]. Due to the subsequent work that followed, it is now well accepted that bone cells modulate their responses to dynamic mechanical stimuli through various parameters of applied strain, namely the magnitude, rate, and duration of the applied mechanical load [2,21].

The concept of a "mechanostat" for bone adaptation to strain was first introduced by Frost in 1987, and then subsequently updated again in 2003 [22,23]. He proposed the idea of a minimal effective strain with several thresholds to delineate the response of bone to specific amounts of strain. Between 50 and 100 με, bone would be weakened and resorbed. Strains from 100 to 1000 με represent a window for positive remodeling to naturally acceptable whole-bone strength. Bone strains greater than 3000 με would cause microdramage, and strains centered near 25,000 με would cause fracture in a young healthy adult. This mechanostat concept was correlated with different types of physical activities that could maintain or strengthen bone, such as bicycle riding (291 με), walking (393–557 με), zigzag running (1147–1226 με), sprinting (2104 με), and forward jumping (1600–3450 με) [1].

In daily activity, however, the human body experiences far smaller strain magnitudes at much higher rates. Huang et al. and Fritton et al. found that the human skeleton experienced strains less than 10 με thousands of times per day, as opposed to large strains exceeding 1000 με which only rarely occurred on a routine basis [24,25]. Subsequent studies demonstrated the importance of these high-frequency low-magnitude strains that could maintain and even build bone. Weinbaum et al. demonstrated that 250 με at 15 Hz produced a fluid shear stress that was 3.75 times that of a 1000με at 1 Hz stimulus, and was sufficient to surpass the threshold for excitation of osteocytes [26]. Rubin et al. was able to double the rate of bone formation with even lower strains of less than 10 με applied at higher frequencies of 10–100 Hz [27]. The results of these studies pointed to the importance of LMMS in their role for bone adaptation and maintenance, concluding that it was the constant mechanical strains due to postural muscular contractions were as if not more effective at maintaining bone mass than the high-amplitude strains of locomotion and rigorous physical activity [28]. This was one explanation for the real-world observable examples of why astronauts lose bone mass in microgravity despite strenuous exercise, and conversely why bed rest patients can maintain bone density with just 3 h of quiet standing per day [6,9].

4. Animal studies

One of the first animal studies to demonstrate evidence for the anabolic effects of high-frequency LMMS was conducted in mature female sheep that were given brief mechanical stimulation treatments daily for 1 year [29,30]. Treated sheep showed a 30% increase in trabecular density and volume of the femur when compared with controls. These results showed how extremely small <10 με events could generate the necessary downstream signals for bone formation [4].

Studies in rats have shown similar anabolic effects of LMMS. To study bone formation in disused limbs, one study showed that a daily exposure to 10-min of LMMS to hindlimb unloaded adult female rats restored bone formation to levels seen in age-matched, weight-bearing control animals [31]. Several other studies demonstrated the efficacy of mechanical signals in bone loss associated with estrogen-deficiency. Ovariectomized mature female rats exposed to LMMS increased their trabecular bone formation by 159% and showed improved biomechanical strength through concomitant increases and decreases in periosteal bone formation and endocortical resorption, respectively [32,33]. LMMS has also been studied in rats for the purposes of fracture healing. Ovariectomized rats given 15-min daily treatments of LMMS were found to have improved callus density at the fracture site, enlarged callus area and width, accelerated osteotomy bridging, upregulated osteocalcin expression, and suppressed osteoclast activity at 30 days [34]. Another ovariectomized rat model for fracture healing showed improved bone stiffness and endosteal and trabecular bone densities in combined mechanical stimulation and estrogen treatment, as opposed to pharmacologic therapy alone [19,34].

The turkey ulna model demonstrated that bone can be maintained along a nonlinear relationship between strain magnitude and frequency [35]. Bone was maintained at four cycles per day of 2000 με, 100 cycles per day of 1000 με, or hundreds of thousands of cycles per day of signals below 10 με. When graphed as a threshold, strain magnitude and frequency that fell below this line resulted in bone loss, whereas regimens above this threshold