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# Bone Cell Response to Physical Activity

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## Bone & Physical Activity: Mechanical, Biochemical and Cellular Aspects

The basic morphology of the skeleton is determined genetically, but is final mass and architecture is modulated by several factors, as biomechanical, nutritional, and hormonal factors. Physical activity is accepted to play a major role in the development and maintenance of bone mass and resistance [1,2]. Physical activity has two bone fracture risk reducing effects: it increases resistance by raising bone mineral content (BMC) and improves bone quality by inducing changes in bone geometry and architecture. It can also reduce fall risk by improving muscle strength and balance. One of the main effects of physical activity on the bone is due to cell response.

## Bone Cell Response to Physical Activity

Mechanical effort on the bone is an important stimulus for bone growth and remodeling, which are also induced by muscle pressure and tension [3]. The cell membrane has certain areas which respond to such mechanical stimuli. These stimuli are translated into stimulus-proportional intracellular signals, so mechanical-sensitive areas are formed in the cell membrane of fibroblasts, osteoblasts and osteocytes, muscle cells, and capillary endothelial cells. Mechanical transducers of these areas respond to mechanical overload both in the form of strength and pressure [4].

Due to their number and physical connections, osteoblasts, lining cells, and osteocytes are morphologically well placed to feel changes in bone mechanical overload and are also connected through gap junctions to channel such stimuli via second messengers. The initiation of the second messenger's effect occurs close to or inside the cell membrane through the transformation of extracellular stimuli, whether mechanical or chemical, into intracellular messages. Mechanical stimulus in the bone creates electric loads which also mobilize calcium and phosphorus. At the same time, these mechanical forces are able to stimulate the release of various cytokines [5].

While at the local level, the generation of electric potentials through piezoelectricity — originated by the deformity of the crystalline material and through capillarity — would stimulate collagen fibers so that they would be oriented in the direction of the forces with subsequent mineral deposit, at the systemic level, cytokine production would stimulate osteoclast activation induced osteogenesis [1].

Physical overload provides a large array of mechanical stimuli in the bones (compression, distension, and torsion forces) which generate small micro potentials in the intraosseus tissues with a piezoelectric effect. Other flow micro potentials are also created as a result of the increase in blood flow through the bone vessels due to the intermittent contamination of the surrounding muscles.

These two types of micro potentials are not sufficient to produce a significant effect on the bone. However, when combined, they stimulate both procollagen secretion by osteoblasts and the calcium crystal deposit in the bone matrix.

The most relevant studies were carried out by Frost, who proposed the mechanostat theory, distinguishing modeling and remodeling mechanisms and determining the bone tissue formation threshold, thus providing with a theory for osteopenia and osteoporosis pathogenesis [6,7].

When local mechanical signals in the bone are in the upper range of this threshold, the bone will be subject to a structure-changing remodeling to reduce local tension under the so-called "minimum effective force." If mechanical loads on the skeleton are very high, bone tension will push it towards a pathological overload area causing a deformation in bone tissue surface. Frost suggests that certain hormones and biochemical agents alter this system by changing the physiological threshold limit allowing for significant bone mass and strength increases.

Mechanical transduction or conversion of a biophysical force into cell response plays a crucial role in many tissues' physiology, including the bone. The response and adaptation to local physical stimuli allow living beings to respond to their environment.

Mechanical stimulus initiates a cascade of intercellular steps following the activation of the mechanosensor in the cell membrane. In less than 100 milliseconds, the phosphatidyl-inositol 4,5-bisphosphate-phospholipase C (PIP2-PLC) complex produces two intracellular messengers: inositol 1,4,5-trisphosphate (IP3), which releases intercellular calcium, and diacylglycerol (DAG), which perpetuates the chain that will form various prostaglandins (PGE2/PGI1). Intermediate steps include protein kinase C (PKC), phospholipase A2 (PL-A2) and arachidonic acid (AA). Also B-catenin, and mTORC2 are included

These intracellular messengers are also activated by hormones such as calcitonin and parathormone, but the receptors activated are not in the same membrane area as mechanical transducers. Both through the 3,5-cyclic adenosine monophosphate (cAMP) pathway, activated by the Gs-protein GTP complex (Gs-GTP), and through the PGs pathway, insulin-like 1 growth factor (IGF-1) is activated, which along with other growth factors, will induce an adaptive remodeling within the bone.

The mechanical stimulus acting on the periosteal matrix is thus transformed into a cellular signal impacting both the quality and quantity of the human skeleton which in turn demands appropriate nutrition and hormonal balance. This allows for a better comprehension of control mechanisms for bone modeling and remodeling [4,6,7].

There is increasing evidence that weight overload is the most significant functional factor, both on bone mass and architecture. It exerts its influence through dynamic stimuli within the bone tissue itself. Both mechanical adaptive modeling and remodeling are homeostatic mechanisms to regulate bone function in each site of the skeleton. Longitudinal curvature and cross shape increase functional overload more than they reduce it. Therefore, the bone's overload adaptive response results in functional stimuli which are both uniform in distribution and minimum in magnitude [8].

Such stimuli are particularly osteogenic and complement a complex genetic program which regulates global shape, soft tissue anchoring, and the relative proportion of trabecular and cortical bone in each bone, which should be adapted to its function. These stimuli's response to such overload is saturated after various cycles, which is necessary for adaptive modeling and remodeling [4].

## Mechanical transduction steps in the bone include four well-defined stages [4,9,10]

**Mechanical coupling:** *In vivo* mechanical loads produce bone deformations which stretch bone cells and create fluid movements within bone canaliculi. The release of second messengers in these stimulated cells has been detected *in vitro*. Bone tissue can detect tensions and respond to them following local deformities, which creates a movement of fluids inside the bone canaliculus with mobilization of the matrix interstitial liquid. Various studies confirm that the bone's internal liquid flow plays a significant role in mechanical transduction in cellular signals. This increases electric potentials which can induce a response in the osteoblasts, including the activation of voltage channels in the cellular area. In parallel, after being stimulated, bone cells can produce second messengers with PLC, IP3 and DAG increase.

**Biochemical coupling:** There are various transduction mechanisms from mechanical signals to biochemical responses with cationic changes in the cell membrane, G protein dependent stimulus and cytoskeleton and phospholipase C or A binding.

The transduction pathway is not known with accuracy, but it may play a significant role in the matrix cytoskeleton. Cells generate an internal force at the level of the cytoskeleton, which in turn exerts greater tension on the extracellular matrix. This internal tension generates a stimulus over the cell adhesion site through integrin proteins [11]. Integrins are a family of heterodynamic glycoproteins binding the extracellular matrix components to the cytoskeleton actin. The binding of integrins to matrix proteins has to overcome these cell tension forces which induce changes in cytoskeleton structure. Owing to this tension, physical stimuli would be rapidly transmitted to the nucleus, potentially changing genetic expression, since it expresses a nexus between the extracellular matrix and the bone cells' genome, which suggests other epigenetic regulation means for this genome, including phenotypic expression [12].

Another potential mechanism for mechanical transduction in the cell membrane involves the guanine-nucleotide binding protein or Gs protein. The role of nitric oxide in bone cell response to overload-induced tensions has also been recently acknowledged [13].

All these pathways are not independent as they are highly associated with others, which could suggest that the whole cell is a mechanosensor and that there are many pathways allowing for mechanical signal transduction.

**Cell to cell transmission of the biochemical signal:** Osteocytes and other cells act as mechanical sensors and communicate signals via cellular connections linked by gap junctions to the effector cells (osteoblasts and osteoclasts). They also produce paracrine factors which may cause osteoprogenitor cells to be differentiated into osteoblasts. There are two potential pathways for a biochemical signal in the sensor cell to be propagated to the effector cell in order to increase osteogenic activity following a mechanical stimulus. Osteoblasts increase matrix protein expression and production in response to mechanical traction, whereas osteoprogenitor cells do not respond to overload in the same fashion as osteoblasts. This suggests that the mechanical environment is important in maintaining bone cell phenotype differentiation. The paracrine communication of the mechanical signal demands various substances to be produced, such as $PGE_2$, prostacyclins, and transforming growth factor beta (TGFβ), which has a significant anabolic effect on the bone as it stimulates alkaline phosphatase activity and collagen synthesis. This could also explain PTH's and nitric oxide's anabolic action.

**Effector cell response:** Overload effects depend on the magnitude, duration, and rate of the overload applied. This overload should be cyclic in order to stimulate new bone resorption and subsequent formation. Osteogenic effects of mechanical overload are reduced with age. Mechanical overload not only inhibits bone resorption; it also enhances bone formation through the endocrine and paracrine effects already described, which increases bone modeling following mechanical stimulus, with successive effects on Frost's bone morphogenetic unit, where other hormones directly or indirectly linked with mechanical loads, such as estrogens, play an important role [14]. The fact that this effect is more clearly detected in young cells could explain osteoporosis' pathogenesis as an aging-associated effect [15]. In conclusion, evidence suggests that regular physical activity, especially if initiated in childhood and adolescence, is the best safe, inexpensive, largely accepted easily accessible method to improve bone strength and reduce fall tendency [16].

Physical activity should be a key part of any strategy attempting to reduce the startling increase in osteoporotic fractures [17]. However, all these fracture-prevention methods require other complements, such as nutrition and avoiding already known risk factors [18]. As a result of this, we should all consider walking as a necessary habit, both when we are young and old.

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