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Review Article

Hylonome

Principles in bone physiology

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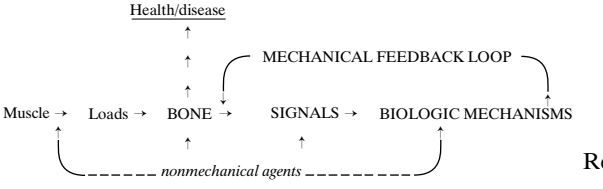
Abstract

The view that nonmechanical agents dominate control of osteoblasts and osteoclasts and thus postnatal changes in bone strength and mass (agent → effector cells → disease) is obsolete. Nonmechanical agents include hormones, calcium, vitamin D, cytokines, gender, genetics, etc. This paradigm overlooks all tissue level features, biomechanics and relationships found after 1960. This more recent information led to the Utah paradigm of skeletal physiology, proposed by Harold Frost in 1995. The Utah paradigm's view is that mechanical factors dominate control of the biologic mechanisms that control changes in postnatal bone and mass. Nonmechanical agents could help or hinder the influence of the mechanical factors but could not replace them. The simplified scheme is as follows:



Relation 1

New evidence supports the Utah paradigm which we view as a supplement to many former views, not as a negation of them.

Keywords: Bone Physiology, Mechanostat, Utah Paradigm, Modeling, Remodeling

Introduction

In the 1960 paradigm of bone physiology that many still hold, the main role of osteoblasts and osteoclasts is to determine bone health and diseases. Bone status depended on those cells and their being influenced by nonmechanical agents like hormones, calcium, vitamin D, cytokines, gender, genetics, etc[1]. The simplified scheme of the relationship is as follows (Relation 2):

Nonmechanical stimulus → effector cell → skeletal health/disease

Relation 2

This paradigm overlooked all tissue level physiologic features and vital biomechanics. It became apparent to Harold Frost that there were deficiencies in this paradigm, which led them to generate the Utah paradigm of skeletal physiology[2-4, 12, 13] in 1996.

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Summary of the newer Physiology

Bones must endure voluntary physical activities without breaking or causing pain, and physical biologic factors must make them strong enough to maintain their load-bearing capacity [3,4].

I. Physical determinants of bone strength[5,6]

1) The properties of bone as a material affect its strength. They vary relatively little with age, disease, sex and species.
2) A whole bone's strength depends on the mass factor, the cross-sectional amount of bone which bears the bone loads.
3) A whole bone's strength also depends on the architectural factor, the size, shape and distribution of its tissue in space.
4) Bone strength depends on the amount of microdamage.

II. Biologic determinants of bone strength[7-9].

1) With the exception of longitudinal bone growth, modeling drifts and remodeling basic multicellular units (BMUs) provide the main postnatal modifications that affect the mass of architectural factors in bone strength.

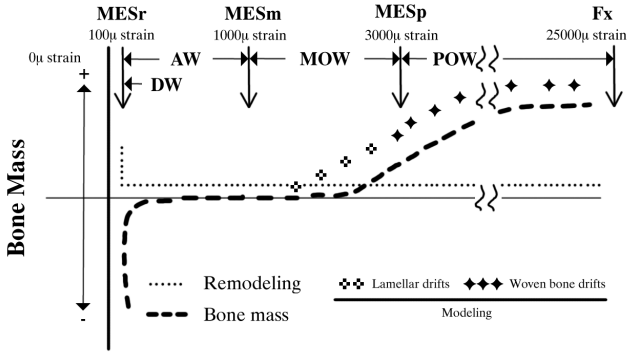


Figure 1. A diagram illustrating the relationship of strains and adaptive responses.

2) Global modeling by drifts (resorption and formation drifts) can increase but not decrease bone mass and strength. "Global" means averaged over a whole bone or skeleton (modeling – dependent bone gain).
3) Global remodeling by BMUs (A → R → F) turns bone over in small packets. The best known products of BMUs are secondary Haversian Systems. Remodeling can take place in either the conservation or disuse modes. In conservation remodeling, resorption equals formation. In disuse mode, remodeling BMUs make less bone than they resorb, a net loss of bone next to marrow. The latter mode is the usual condition with aging (remodeling-dependent bone loss).
4) Remodeling repairs bone microdamage by removing and replacing the damaged bone with new bone. Failure to do so can cause fatigue fractures of trabeculae and whole bones because of the accumulation of damage.

In summary, bone mass increases during growth because longitudinal and circumferential bone growth and modeling add bone faster than remodeling removes it. Bone mass declines in most adults because longitudinal bone growth, and cortical bone modeling that can increase it, stops, but the remodeling that can decrease it continues. Losses of spongiosa next to marrow occur at birth and continue until death, while loss of cortical bone next to marrow occurs in the adult skeleton with aging.

The Role of Muscle in Bone Mass and Strength[11-13]

The largest loads of bone come from muscles. Studies of the bone/muscle relationship in 1,066 humans by three groups shows the same high correlation ($r=0.89$-0.94; $p<.00001$).

Frost 's Mechanostat Theory[2-4, 9, 12, 14]

The mechanostat theory begins with the concept, originally proposed by Frost in 1964, that there is a minimum effective strain (MES) which must be exceeded to excite an adaptive response to mechanical overload. He suggests that there is a range of strain values that will evoke no response. Strain above this range will evoke increased bone (a positive adaptive response) and strain below this range will cause a loss of bone (a negative adaptive response). He further states that modeling-dependent bone loss is stimulated at strains above 1500 microstrain, whereas remodeling-dependent bone loss is stimulated when strains fall below 100 microstrain (Fig. 1).

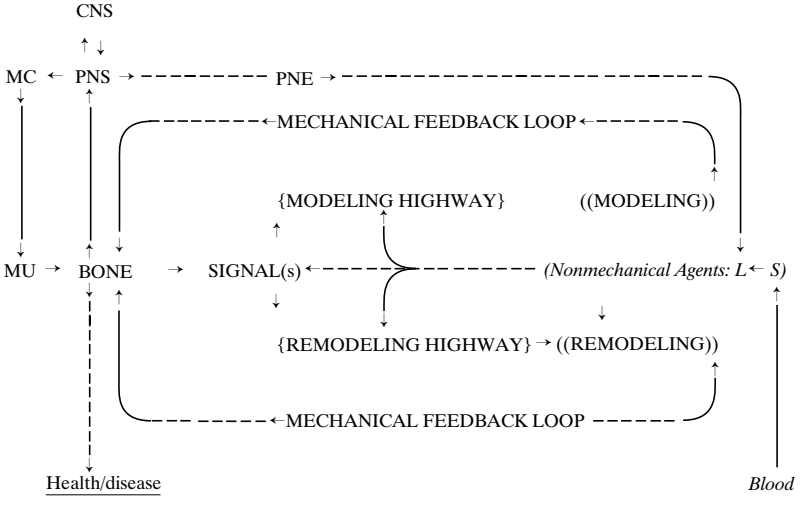
Because modeling and remodeling are stimulated at different strain ranges, they are not stimulated at the same time on the same surface.

The Mechanical Usage Feedback Loop[2-4, 9, 12, 13]

An important concept that limits the extent of the response to a given stimulus, as well as limiting the transient response to a given stimulus, is the mechanical usage feedback loop. For example, a given dose level of an anabolic agent like (PGE_2) evoke an increase in bone for some 30 days (transient) which stabilizes at steady state thereafter with continual treatment. The increase in bone mass has kicked in the negative mechanical usage feedback loop opposing any further addition of bone, because added bone will lessen the bone strain. Another example of the negative feedback loop in action is the loss of PGE_2- induced bone gain on discontinuation of treatment[15, 16].

The Mechanostat System and the Utah Paradigm[2, 4, 9, 12-14]

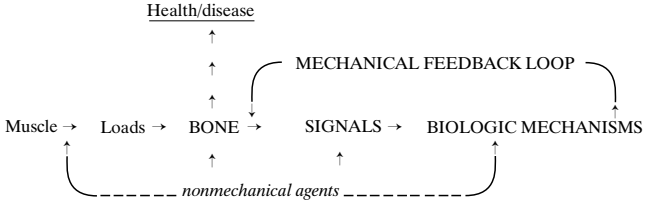
Pondering how the mechanostat system functions in bone physiology led to Frost's development of the Utah Paradigm of skeletal physiology. For the skeleton (bones), the bold-face caps in Relation 3 identify the mechanically-dedicated message traffic and feedback in the mechanostat, which is part of that paradigm. CNS=central nervous system; PNS=peripheral nervous system; PNE=peripheral nervous endings; MC=muscle contractions, MU=mechanical usage; L=local nonmechanical agents; S=systemic, blood-borne



Relation 3

nonmechanical agents; mechanical feedback loop (m) applies to modeling; mechanical feedback loop (r) applies to BMU-based remodeling. Italics signify the nonmechanical things that can affect the mechanically-dedicated message traffic, but which are not a part of it.

A simplified scheme is seen in relation 4. Nonmechanical agents, like growth hormones, androgens, calcium and vitamin D, affect muscles and thus indirectly affect the bone loads and strains that help to control the biologic mechanism. The feedback is negative, since responses to most "error signals" tend to reduce the errors and signals.



Relation 4

The Utah paradigm of bone physiology suggests four conditions:

1) The biologic mechanisms that determine skeletal health and disease need effector cells and nonmechanical agents in order to work.
2) Mechanical factors guide those mechanisms in time and space;
3) After birth, neuromotor physiology and anatomy dominate control of those biologic mechanisms; and
4) Most nonmechanical factors can help or hinder but cannot replace or duplicate the mechanical control.

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