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Perspective Article

Hylonome

The benefit of combining non-mechanical agents with mechanical loading: a perspective based on the Utah Paradigm of Skeletal Physiology

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Abstract

The Utah Paradigm of Skeletal Physiology with its key component, the mechanostat hypothesis, suggest plausible explanations of some of the tissue-level changes occurring from combining selected non-mechanical agents (anabolic and anti-resorptive/(re)modeling agents) with mechanical loading (osteogenic exercise) to increase bone mass and strength. The evidence for combining selected anabolic agents like parathyroid hormone, prostaglandin E_2, growth hormone, etc. with mechanical loading can increase bone mass is strong. Anabolic agents influence loading-related bone formation changes in a permissive manner and modulate (increase) the responsiveness of bone tissue to mechanical loading by changing thresholds for bone formation and resorption. However, any beneficial effect of combining selected anti-resorptive/(re)modeling agents like estrogen with loading is marginal, especially in adult skeletons. Postulated changes in modeling and remodeling thresholds (set points) and known direct effects on bone cells by non-mechanical agents may explain the observed tissue-level changes associated with large and minor increases in bone mass. Although the pharmaceutical industry has avoided considering osteogenic loading in the treatment of osteoporosis, a methodical dose-response study of anabolic agents combined with loading should: (1) provide opportunities for therapeutic intervention to imitate or enhance the osteogenic response to loading in order to correct osteopenias; (2) provide the potential to diminish the dosage of drugs required to induce bone formation in ways that enhanced efficacy and reduced any side effects; and (3) improve the quality of life and reduce the risk of falls by improving balance, gait speed and muscle strength with a non-mechanical agent like GH that could improve both muscle and bone mass and strength. Lastly, more studies are needed which determine bone strength instead of only "mass" in aged skeletons so one can assess how effective such treatments would reduce the risk of fracture in the clinic.

Keywords: Non-mechanical Agents, Mechanical Loading, Mechanostat, Set Point, Utah Paradigm

Why combine non-mechanical agents with mechanical loading?

We know physical activity causes relatively larger changes in bone mass and strength in children than in adults and it has been only marginally effective for improving bone density on older adult skeletons[1,2]. The decreased effectiveness in the aging skeleton may be attributed to a reduced sensitivity of bone tissue to mechanical stimuli[3,4]. One strategy to overcome the poor response in the aged skeleton might be to administer permissive non-mechanical agents[5-8] to overcome that decreased sensitivity and synergistically or additively increase bone mass and strength.

Numerous non-mechanical agents are necessary for growth, maintenance and repair of bone mass. Among them are so-called anabolic agents and so-called anti-resorptive/(re)modeling agents. For example, anabolic agents like parathyroid hormone (PTH) increase bone mass by adding bone on all envelopes. It is well established that estrogen helps to maintain bone mass by depressing bone resorption. Some selected permissive, non-mechanical agents like parathyroid hormone (PTH), growth hormone (GH) and

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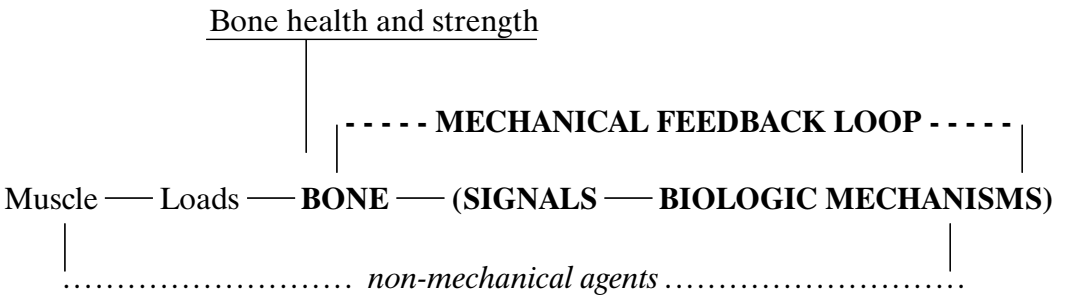

Figure 1. Frost's simplified scheme of the Utah Paradigm of Skeletal Physiology. The "signals" is the mechanostat, the biologic mechanisms include the adaptive mechanisms involving mainly modeling and remodeling. In a recent conversation with Frost, he considered the mechanostat to include what is in the parenthesis, the signaling and biologic mechanisms (modified from Frost[12]).

estrogen decline with age in humans and rats. Since age-related decreases in specific non-mechanical agents may also cause the decreased sensitivity of bone cells to mechanical stimuli, this perspective reviews the effects of supplementing selected non-mechanical agents with mechanical loading in growing and aged human and rat skeletons. The perspective determines whether those agents are permissive for skeletal mechanotransduction and modulate the responsiveness of bone cells to loading by changing the thresholds for bone formation and resorption as detailed in the "Utah Paradigm of Bone Physiology"[6,7,9-15] (Figure 1).

Although much was written about the cellular basis of these selected non-mechanical agents and mechanotransduction responses, and about their signaling pathways, cytokines and growth factor production, etc., this perspective will not discuss those matters limiting the discussion to tissue-level responses.

The interaction between non-mechanical agents and mechanical loading

Historical. The beneficial effects of combining mechanical loading and anabolic agents were first suggested by Lent Johnson as early as 1965[16] in a report that sodium fluoride (NaF) resulted in an early bone-anabolic response in bone sites under mechanical loading in man. This idea lay dormant until Baylink and colleagues beginning in the '80s noted in a series of articles that NaF increased bone mass in high mechanical loading sites in the lower extremities[17-20]. They noted in man a lack of ^{99m}Tc bisphosphonate uptake in poorly loaded extremities from NaF administration. In NaF treated subjects, Riggs et al. also noted decreased bone mineral density in the less loaded radial shaft, but measured BMD in more heavily loaded sites (lumbar spine, femoral neck and trochanter)[21].

The above findings attracted few followers mainly because NaF was considered a questionable agent that produced excessive osteoid, possibly due to delayed or defective mineralization. Also most bone researchers as well as the pharmaceutical industry avoided considering mechanical loading as a regulator of modeling and remodeling-dependent bone gain activities. Furthermore, the concept of bone cell activity under endocrine control had become deeply entrenched, and research utilizing cell, tissue and organ culture systems free from mechanical loading effects were encouraged and well funded and that discouraged research in this area[22].

The interaction of selected anabolic agents (PGE_2, PTH and GH) and mechanical loading

In a previous article, I reviewed the effects of the interactions of prostaglandin E_2 (PGE_2), parathyroid hormone (PTH) and growth hormone (GH) with mechanical loading[23]. An update follows.

Prostaglandin E_2 and loading. Our studies of PGE_2 effects repeatedly revealed a greater osteogenic response in the more heavily loaded parts of the rat skeleton[24-29]. The extremities were most responsive and the long bones of immobilized rats responded much less than the controls. In dogs, there was heavy uptake of ^{99m}Tc bisphosphonate in the loaded extremities and poor uptake in the skull region[28]. Furthermore, Tang et al. in a dose response study of PGE_2 combined with external loading showed that 1mg PGE_2 /kg/d combined with a minimum effective load by four-point bending of the mid-tibial shaft had a synergistic effect on periosteal and an additive effect on endocortical bone formation[30]. Recently we exercised rats by raising their cages to enforce a bipedal stance for feeding and drinking. We found that 1 mg PGE_2 /kg/d and raised cages had the same cortical bone effects reported by Tang et al.[30], as well as an additive effect in increasing trabecular bone mass[31].

Parathyroid hormone and loading. The literature on the results of combining PTH with loading supports the beneficial effects of such treatment. Gasser et al. noted the unloaded vertebral bodies in rats responded poorly to PTH administration[32]. In the same vertebrae, Chow et al. found a synergistic effect of PTH and mechanical loading that increased bone mass[33]. More recently, three groups reported synergistic increases in cortical bone mass with such com-

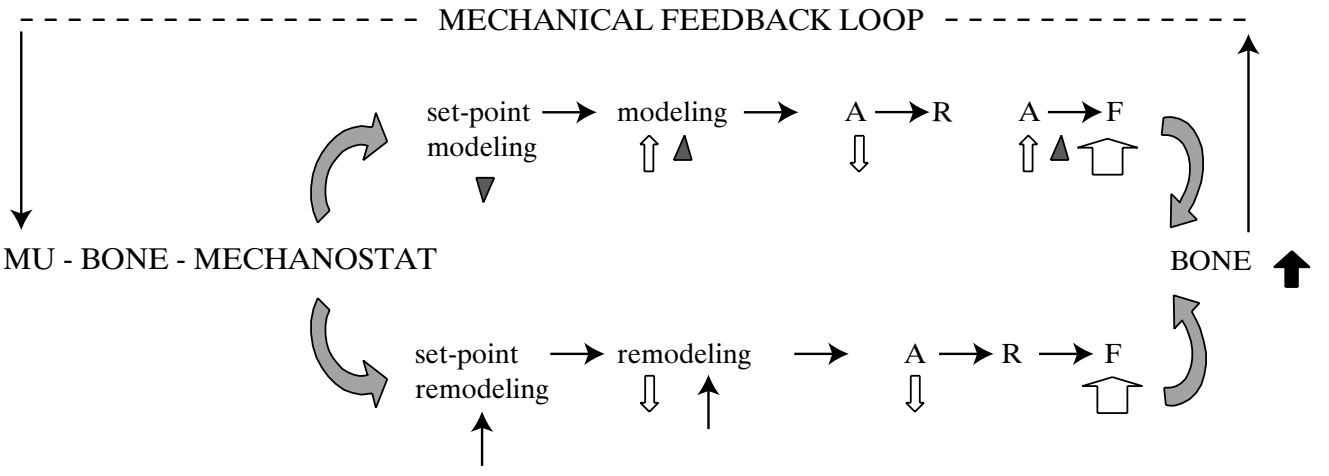

Figure 2. The Utah Paradigm of Skeletal Physiology suggests a plausible explanation of the beneficial effects of combining an anabolic agent (PTH or PGE_2) with mechanical loading (osteogenic exercise).

Increased mechanical loading (osteogenic exercise): (1) stimulates formation drifts [modeling] (⇧); and (2) depresses bone resorption [(re)modeling and resorption drifts] (⇩); responsiveness as follows: children>>>adults.

Anabolic agents: (3) lower modeling set point (▼) to enhance loading-induced modeling-dependent bone gain (▲) ➔ positive bone balance; (4) raise remodeling set point (↑) ➔ increase disuse-mode BMU remodeling (increase ↑ in number of BMU remodeling units), thus increase remodeling space ➔ negative bone balance; and (4) a "direct" stimulation of osteoblastic activity that increases mineral apposition rates of formation drifts (⇧) and stimulate BMU units with formation (⇧) exceeding resorption ➔ (increase in mean wall thickness) ➔ positive bone balance (positive-mode BMU remodeling). It is not known whether loading can result in positive-mode BMU remodeling.

Net result: There is a synergistic increase in periosteal bone formation (modeling-dependent bone gain) and an additive increase in endosteal bone formation (remodeling-dependent bone gain) from the combined treatment which coupled with depression of bone remodeling from loading results in marked increase in bone mass (Bone ⇧).

Note: ↓ = decrease; ↑ = increase; mu = mechanical usage or loads; small open arrow = loading effects; large open arrow = direct anabolic agent effect; solid arrowhead = anabolic agent effects.

bined treatment[34-36]. In addition, Cann et al. found trabecular bone density was higher in the regions of lumbar vertebrae under the highest compressive loading forces in women[37].

Growth hormone and loading. The combination of growth hormone (GH) with mechanical loading added more support for the beneficial effect of such treatments. This section will cover GH and the insulin-like growth factor 1 (IGF-1), because GH levels could alter the cellular microenvironment by direct action on osteoblasts or indirectly through GH induction of IGF-1[38].

The GH literature dates back to 1994, when Yeh et al. reported that GH potentiated the effect of treadmill exercise on tibial cortical bone formation[39-41]. This study resulted in a synergistic interaction in both cortical surfaces (endosteal and periosteal). Oxlund et al. also showed that GH and treadmill exercise markedly enhanced cortical bone formation and strength in older rats[42]. Mosekilde et al., using voluntary exercise with GH administration, found an additive effect at all sites studied (vertebrae, femoral diaphysis, neck and distal metaphysis)[43]. The main effect was increased periosteal new bone formation. More support for the beneficial effect of GH in enhancing loading responses was found by Halloran et al. and Forwood et al. who found impaired GH responses of trabecular and periosteal and endocortical bone formation during skeletal unloading[44] in Lewis Dwaft rats[8]. In comparison, loaded Dwaft rats GH increased endocortical bone formation and periosteal woven bone formation.

I could find only one abstract on loading and IGF-1 administration. Gross et al.[45] found the combination synergistically enhanced periosteal bone formation by 5-fold. The bulk of their paper dealt with muscle mass and structure and did not deal with the interaction between bone mass and strength. This was unfortunate in that this was an excellent opportunity to add to our knowledge on the interaction between bone and muscle (the bone/muscle unit) in the Utah Paradigm for Bone Physiology[11,46,47].

The interaction of a selected anti-resorptive/(re)modeling agent (Estrogen (E_2)) and mechanical loading

Estrogen and loading. A number of studies that explored whether exercise and estrogen replacement therapy in women

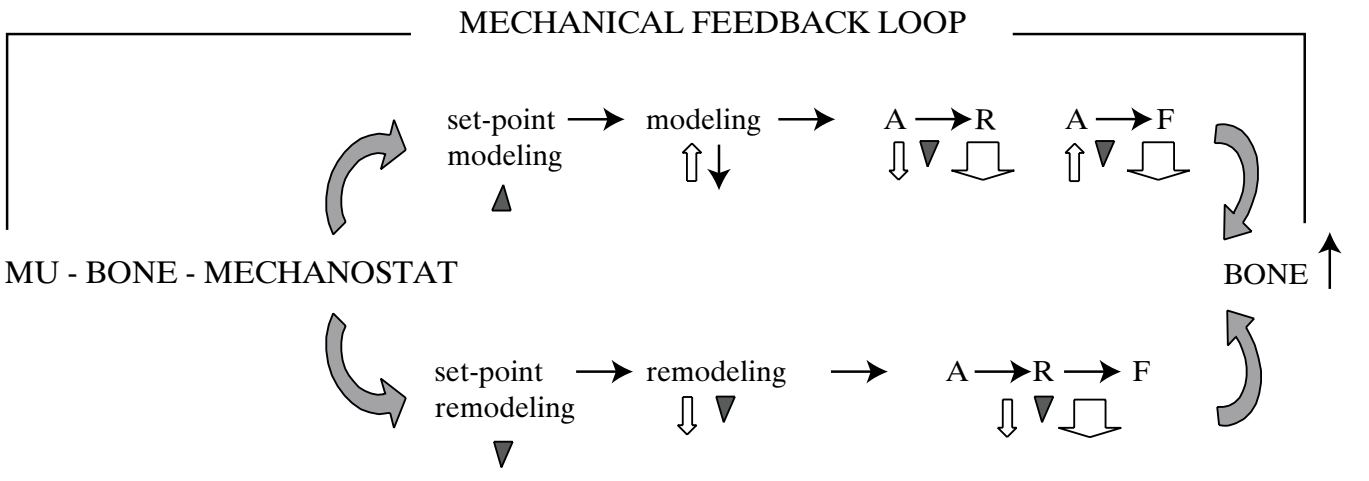

Figure 3. The Utah Paradigm of Skeletal Physiology suggests a plausible explanation of the beneficial effects of combining an anti-resorptive/(re)modeling agent with mechanical loading (osteogenic exercise).

Increased mechanical loading (osteogenic exercise): (1) stimulates formation drifts [modeling] (⇧); and (2) depresses bone resorption (⇩) [responsiveness as follows: children>>>adults].
Anti-resorption/(re)modeling agents (estrogen): (3) raise modeling set point (▲) to enhance loading-induced modeling-dependent bone gain (▼) → slight positive bone balance; (4) estrogen lowers the remodeling set point to depress bone resorption → reduction in resorption drift (⇩) and remodeling space (⇩) → slight positive bone balance and blunt the loading-induced formation drift.
Net result: Increased bone mass due to reduction in modeling and remodeling space, but estrogen partially abrogates loading-induced bone formation resulting in marginal increase in bone mass in the adult skeleton. More increases in children because they are more responsive to loading-induced bone formation.

Note: ↓ = decrease; ↑ = increase; mu = mechanical usage or loads; small open arrow = loading effects; large open arrow = direct estrogen effect; solid arrowhead = estrogen effect.

have additional or synergistic responses suggested that the effects of estrogen and loading are additive[48-51]. There is no evidence that there is any synergism between them[52].

It has been established that estrogen maintains bone mass through depression of bone resorption. Whether estrogen facilitates the bone anabolic response to increased mechanical loading is unclear[49,53-65]. In contrast, Turner et al. indicated it reduces periosteal bone formation in rapidly growing rats[65,66], followed by several reports that estrogen dampens periosteal modeling response to loading in older female rat skeletons[67-69]. It is common knowledge that ovariectomy leads to increased bone formation in all envelopes, which could suggest estrogen decreased bone formation. Wronski et al. concluded estrogen replacement reduced absolute bone formation but enhanced net bone formation[70,71].

The above findings could suggest that estrogen administration suppressed and ovariectomy enhanced mechanically-induced osteogenesis[63]. There is no direct evidence that estrogen enhances the responses of bone cells to loading. The available evidence suggests estrogen has no or a depressive effect on the adaptive response to loading by individual cells. This led Lanyon and Skerry to hypothesize that it is not estrogen that is necessary for a competent adaptive response to load bearing but the estrogen receptor[52,72-74].

The relationship to the Utah Paradigm of Skeletal Physiology and the effect of combined non-mechanical agents and loading — the tissue level responses

The Utah Paradigm of Skeletal Physiology suggests one possible explanation of the beneficial effects of combining an anabolic agent (PTH or PGE_2, etc.) with mechanical loading (osteogenic exercise; Figure 2). It is well established that increasing mechanical strain from osteogenic loading alone will turn on modeling-dependent bone gain and depresses re(modeling)-dependent bone loss resulting in a modest increase in bone gain and strength[76-84]. On the other hand, anabolic agents have been postulated to influence loading-related bone formation in a permissive manner and modulate the responsiveness of bone tissue to mechanical loading by lowering the modeling[6,8,12,30,85] and raising the remodeling set points. Lowering the modeling set point will turn on modeling-dependent bone gain while raising the remodeling set point will turn on (re)modeling-dependent bone loss. In addition, there are known direct effects of anabolic agents stimulating osteogenic cells and in such a manner as to stimulate the bone formation phase of remodeling resulting in BMU remodeling-dependent bone gain and enhance formation

drifts[28,29,75-78]. The net effects of combining an anabolic agent with mechanical loading are synergistic increases in modeling-dependent bone gain (increased periosteal bone gain), additive increase in endosteal bone gain and decrease remodeling and resorption drift. The multiple actions of anabolic agents and mechanical loading stimulate bone formation along with the mechanical loading-induced depression of bone resorption resulting in a favorable positive bone balance and thus a marked increased in bone mass and strength. The above responses suggest that not only the mechanostat thresholds or set point changes are needed, but the direct anabolic effects of anabolic agents need to be factored in to explain the observed findings (Figure 2)[29].

Let us also employ the Utah Paradigm of Skeletal Physiology to explain the observed modest gain in bone mass and strength with combining estrogen with mechanical loading (Figure 3). As mentioned earlier, mechanical loading alone may enhance modeling-dependent bone gain and depressed (re)modeling-dependent bone loss resulting in a modest positive bone balance[76-78]. Anti-resorptive/(re)modeling agents like estrogen have been postulated to lower the bone remodeling set point to depress bone resorption; which reduces resorption drifts and remodeling spaces, resulting in a slight positive bone gain. In addition, estrogen has been shown to inhibit periosteal bone formation (modeling-dependent bone gain) in rat long bones[65] contributing to a slight negative bone balance. Nevertheless, these multiple actions favor a modest positive bone balance that could increase bone mass and strength (Figure 3).

Discussion

One must remember that the chief mechanical function of bones lies in providing enough strength to meet the voluntary mechanical demands on them so as not to fracture[9-13]. Although the evidence for combining selected anabolic agents with mechanical loading to increase localized bone mass in preclinical studies is strong, there is a need for more studies which determine bone strength in order that one can assess how effective such treatments could be in reducing the risk of fracture. Unfortunately only two pre-clinical articles on the effects of combining non-mechanical agents and mechanical loading directly measured bone strength[42,43]. The rest of the articles reported bone mineral density and bone mass values. The bulk of the pre-clinical studies determined regional bone mass in growing bones by histomorphometry of cancellous and cortical bones. Histomorphometric analysis of diaphyseal cortical bone can provide bone distribution data that allows calculation of bone strength, but such data are missing. Furthermore, regional distribution or redistribution of diaphyseal compact bone mass can significantly change the cross-sectional moment of interia (CSMI) with large impact on bone strength with or without change in mass balance[25,28-30,34,77,80-82,86-92]. Thus, it is imperative future pre-clinical studies must determine bone strength not only in growing but in adult skeletal sites.

The clinical studies reported here lack reliable bone mass and strength data. They employed bone mineral density (BMD) as an indicator of bone "health". Bone mineral density values are unreliable indicators of both whole-bone strength and bone mass. Future studies must depend on peripheral quantitative tomography (pQCT) *in vivo* derived bone strength indices (BSI) as indicators of whole bone strength[94-101].

More dose response studies with different anabolic agents and various mild exercises are needed to investigate the therapeutic window for beneficial responses in aged skeletons. Inappropriate exercise such as jumping exercises with a weighted vest were injurious in recruits in whom extensive physical exercise led to large increases in BMD, but 41% of the recruits had stress fractures[93]. Since mild exercise, like walking, alone in older individuals may not increase bone mass, combining it with an anti-resorptive/(re)modeling agent may not be very effective. However systematic studies with anabolic agents and exercise would: (1) provide opportunities for therapeutic intervention to imitate or enhance the osteogenic response to loading for the reversal of osteopenia; (2) provide potential to diminish the dosage of drugs required to induce bone formation which leads to enhanced efficacy and reduced side effects; and (3) improve the quality of life and the risk of falls by improving balance, gait speed and muscle strength with a non-mechanical agent like GH that improves both muscle and bone mass and strength.

More studies are needed which determine or calculate bone strength in aged skeletons so one can assess how effective the combined treatment would reduce the risks of fracture in the clinic.

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