

Editorial

Anabolic Agents and Osteoporosis: Quo Vadis?

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Abstract

There are preclinical studies and limited clinical experiences with bone and muscle anabolic agents (e.g., parathyroid hormone (PTH), sodium fluoride (NaF), prostaglandins (PGs), growth hormones (GH), etc.) that show they have significant advantages over antiremodeling agents in patients with established osteoporosis¹⁻⁵. The strength of anabolic therapy is as follows: it rapidly reverses bone loss in laboratory animal models and humans, the quality of bone with some agents is believed to be normal, an increase in bone strength in animal models, and a reduction of spinal fracture rate with PTH. The weaknesses of this therapy are high cost, poor understanding of mechanism of action, parenteral mode of administration, rapid bone loss following termination of treatment, abnormal quality of bone, lack of tissue specificity, and undesirable side effects. Both animal and clinical studies have shown one can preserve the bone gain following termination of treatment with antiremodeling agents or exercise based on the lose, restore and maintain (LRM) concept⁶. However, the more important efficacy issues which need to be addressed are tissue specificity and reduction of undesirable side effects. This report will address these issues with the suggestions that the potentiation of the mechanical loading osteogenic response by anabolic agents can overcome the disadvantages which accompany the use of anabolic agents. In addition, the possible role of nitric oxide (NO), an agent required for mechanical loading-induced bone formation, will be discussed.

Keywords: Mechanical Loading, Anabolic Agents, Interactions, Bone Formation, Osteoporosis

Beneficial effects of the interaction of mechanical loading and anabolic agent

Since both mechanical loading and anabolic agents activate modeling-dependent bone gain, they have a parallel pattern of modeling response and many common biochemical events and pathways. Among these are: increased intracellular calcium, intracellular cAMP, prostaglandin (PG) and nitric oxide (NO) accumulation, gene expressions of IGF-1, collagen and osteocalcin and connexin-43, etc.⁷⁻¹⁴. It was conceivable that they might act together to increase bone mass and strength, which proved to be true. The beneficial effects of combining mechanical loading and anabolic agents were first suggested by Lent Johnson¹⁵ as early as 1965 (Table 1). He described an early anabolic response of NaF in bone sites under mechanical usage in man. This observation laid dormant until Baylink and colleagues^{4,16-18} reported in a series of articles in the mid 80s that NaF increases bone mass in areas of high

mechanical stress, especially in the lower extremities, and noted the lack of ^{99m}Tc diphosphonate uptake in the poorly loaded upper extremities in man. In addition, Riggs et al.¹⁹ also reported that bone mineral density decreases slightly in the radial shaft while sites like the lumbar spine, and femoral neck and trochanter increased with NaF in man.

The above findings had few followers, mainly because there were few investigators interested in both bone anabolic agents and skeletal adaptation with mechanical usage (i.e., exercise) before 1990. The animal data came in the late 80s when we repeatedly found in our studies with PGE₂ in rats, that there was a non-uniform anabolic response in skeletal sites. The amount of bone gain with PGE₂ was greater in heavily loaded sites (i.e., the distal portion of long bones more than in the spine). Furthermore, our ^{99m}Tc diphosphonate uptake studies in dogs showed poor uptake in the skull and heavy uptake in the extremities²⁰⁻²³.

In addition, Yeh et al.²⁴ reported growth hormone potentiated the effect of treadmill exercise on tibial cortical bone formation; Gasser⁵ showed the poorly loaded tail vertebrae were less responsive to PTH than were other sites in the rat, and Cann²⁵ reported trabecular bone density was higher in the area of lumbar vertebrae under the highest compressive loading force.

Recently, both Chow et al.²⁶ and Tam²⁷ have shown nitric

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	Author	Agent	Species	Evidence
1.	Johnson ¹⁵	NaF	man	earlier response of NaF in areas under mechanical usage
2.	Schulz, et al. ¹⁶	NaF	man	lack of ^{99m} Tc diphosphonate uptake in upper extremity from NaF; response to NaF in the region of lower appendicular skeleton rich in trabecular bone
3.	Schulz, et al. ¹⁷	NaF	man	changes included periosteal and endosteal bone formation as well as trabecular thickening, localized in areas of high mechanical stress
4.	Riggs, et al. ¹⁹	NaF	man	BMD decrease by 4% in radial shaft, compared to 35%, 12%, and 10% increases in lumbar spine, femoral neck, and femoral trochanter
5.	Resch, et al. ¹⁸	NaF	man	increased trabecular bone density on peripheral skeletal site
6.	Ke, et al. ²¹	PGE ₂	rat	The amount of bone formed tibial shaft>distal tibial metaphysis>distal femoral metaphysis>proximal tibial metaphysis>lumbar vertebral body
7.	Li, et al. ²⁰	PGE ₂	rat	more endocortical woven bone proliferation occurred in treated ovariectomized and sham than immobilized rats
8.	Jee, et al. ²³	PGE ₂	dog	skull bones lacked anabolic response; more stimulated bone formation occurred in distal long bones
9.	Yeh, et al. ²⁴	GH	rat	GH potentiates the effect of treadmill exercise on tibial cortical bone formation
10.	Tang, et al. ²⁸	PGE ₂	rat	PGE ₂ and loading had an additive effect on endocortical bone formation and a synergistic effect on periosteal bone formation
11.	Cann, et al. ²⁵	PTH	man	highest trabecular bone density in area of L1 and L2 under highest compressive loading force
12.	Gasser ⁵	PTH	rat	unloaded tail vertebral bodies responded less to PTH
13.	Chow, et al. ²⁹	PTH	rat	PTH potentiates mechanically-induced bone formation in caudal vertebrae
14.	Tam, et al. ²⁷	OSA-117A	rat	OSA-117A increased BMC, BMD and strength when subjected to exercise
15.	Mosekilde, et al. ³⁰	GH	rat	additive effect of voluntary exercise on bone strength
16.	Jamel, et al. ⁴⁴	nitrate	man	more increase in knee-BMD than hip-BMD
17.	Chow, et al. ²⁶	NO	rat	potentiates the stimulatory effect of mechanical loading on bone formation

Table 1. Amplification of mechanical loading-induced bone formation with anabolic agents.

oxide donors and a new peptide, respectively, potentiated the stimulatory effect of mechanical loading on bone formation. However, these agents were found to be necessary, but not sufficient, for induction of bone formation alone.

The most convincing data in support of the beneficial effects of combining mechanical loading and bone anabolic agents were the dose response studies of Tang et al. and Chow et al. with PGE₂ and PTH in rats. Tang et al.²⁸ showed that when 1mg PGE₂/kg/d was combined with a minimum effective load by 4 point bending of the mid tibial shaft, a synergistic effect on bone formation was observed at the periosteal surface, and an additive effect at the endocortical surface. Chow et al.²⁹ found a synergistic effect of PTH and loading in increasing bone mass. They found mechanical stimulation of the eight caudal vertebra induced an anabolic response that was augmented by a single injection of PTH before loading. Furthermore, Mosekilde et al.³⁰ showed an additive effect of voluntary exercise and

growth hormone treatment on bone and bone formation, respectively (Table 1).

The beneficial effects of combining an anabolic agent like PGE₂ and loading might be explained by (1) PGE₂ lowering the modeling and remodeling threshold (i.e., lowering the modeling setpoint); and (2) the effects of local factors induced by either PGE₂ or higher peak strain. One, it has been suggested that anabolic agents can lower the modeling threshold. If this is true, the agent would make a smaller strain (i.e., less mechanical usage) than normal turn modeling drifts on, and decrease remodeling to conserve bone^{5,31,32}. Two, it is known that exogenous PGE₂ induces bone cells to produce insulin-like growth factor 1 (IGF-1), transforming growth factor β (TGF β) and IGF binding protein³³⁻³⁵. Similarly, loading also enhances the production of local factors like IGF-1, TGF β , endogenous PGE₂ and prostaglandin I₂³⁶⁻⁴⁰. If these local factors enhance the function of osteoblasts and accelerate differentiation of osteoprogenitor cells, synergism or addition will result.

Therapeutic implications

The fact that mechanical loading and anabolic agents are additive in bone gain has more value than simply being an academic exercise. This fact strikes at the heart of therapeutic measures for employing anabolic agents to add bone mass.

A better understanding of the interactive effects of mechanical loading and bone anabolic agents is likely to have an important impact on the management of osteoporosis in the near future. First of all, the interaction of proper exercise and anabolic agents can improve the latter therapeutic window (i.e., lower dose requirement, reduce side effects, etc.). Also, the interaction can target the anabolic response to sites at risk with proper exercise (i.e., femoral neck and wrist). Finally, the elucidation of mechanical loading/anabolic activated signaling can lead to the discovery of new bone forming agents.

A role for nitric oxide?

There is a general agreement that PGs are necessary in the induction of bone formation by mechanical stimuli⁷⁻¹⁰. More recently, it has been shown that nitric oxide (NO) production is also required^{11,12}. In vitro, low concentration of NO has been reported to promote the proliferation of osteoblast-like cells and modulate osteoblast function⁴¹. In vivo studies in animal models showed NO synthase inhibitors reduced bone formation rate in the rat tibial epiphysis and the treatment with NO donor nitroglycerin protected rats from ovariectomy - and glucocorticoid - induced bone loss^{11,12,42,43}. More exciting are the studies by Chow et al.²⁵ and Jamel et al. showed exogenous NO potentiates the stimulatory effect of mechanical loading on bone formation, but lacks effect on unloaded vertebrae, suggesting NO alone is necessary, but not sufficient, for induction of bone formation. While Jamel et al.⁴⁴ found intermittent use of nitrates increases bone mineral density in both the hip and knee, the knee more than the hip.

These studies are encouraging, but more studies are needed because current available NO donors are relatively non-specific, and development of more selective agents that could be targeted to the skeleton, or better yet, to bones at risk by combining the NO with mechanical loading is needed. Possibly such studies can elevate NO to a role in the treatment of osteoporosis.

Summary

The major disadvantages of bone and muscle anabolic agents are their lack of specificity to bones at risk and their undesirable side effects. These can be overcome by allowing the anabolic agents to potentiate the stimulatory effect of mechanical loading on bone formation. The fact that mechanical loading and anabolic agents are additive in bone gain can improve the agents' therapeutic window and thus lower dose requirements and reduce side effects. The

interaction can target the anabolic response to sites at risk with proper exercise. Also, the elucidation of mechanical loading/anabolic activated signaling may lead to the discovery of new bone forming agents. In addition, combining nitric oxide with mechanical loading may lead to another approach to the treatment of osteoporosis.

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