## Modulation of Strain Sensing: A New Approach for the Treatment of Osteoporosis

Jürg A. Gasser

Currently available therapies for postmenopausal osteoporosis either aim at correcting the estrogen deficit (HRT, SERMs), specifically target osteoclasts (calcitonin, bisphosphonates) or stimulate bone formation (fluoride). With the exception of HRT [19, 14, 21], which has some preserving effect on muscle mass, all these treatments fail to account for the potential role of decreasing muscle strength in the development of the disease, despite the close association between the decline in muscle strength and bone loss in males and females [19, 1].

During skeletal growth, bone and muscle mass are continuously challenged by the roughly 25 fold increase in body weight. Modeling drifts ensure that bone dimensions can keep up with the increasing forces and thus prevent the bones from breaking [9, 10, 11]. During the growth period, the skeleton is kept in a continuous 'mild overload' situation (MOW) (Figure 1) with strains of around 1000µstrain keeping the modeling drifts active. It is no surprise, that during this period of life, additional exercise is most effective for the build-up of additional muscle and bone strength. Following the cessation of growth in young adults, muscle strength plateaus and starts its slow descent approximately at around age 30 to 40. During that time bone mass catches up and the typical strains bones are exposed to are in the range between 100 and 1000(strain, i.e. the adapted window (AW)(Figure 1). In this situation modeling drifts are switched off and 'normal' remodeling guarantees skeletal maintenance which includes mainly replacement of old bone and microdamage repair.

It has been suggested that estrogen could lower the modeling and remodeling thresholds [15, 2, 8]. If true the hormone would make smaller strains (i.e. less vigorous exercise) than before turning modeling drifts on, and decrease the remodeling rate to conserve bone [11]. Removing estrogen, as happens in the menopause, would thus raise the thresholds suggesting partial disuse to the strain-sensing mechanism (DW, Figure 1), leading to the activation of remodeling to remove bone until the perceived strains fall again into the comfort zone (adapted window, Figure 1). It is indeed intriguing that ovariectomy in rats leads only to transient rapid bone loss [23, 12] through the activation of remodeling. In a second phase bone mass equilibrates at a lower level and bone remodeling returns to a more 'normal' rate.

According to this hypothesis, the postmenopausal estrogen status puts the skeleton into a 'partial disuse' situation with the skeleton experiencing strains in the lower half of the adapted window, and the minimal effective strain for modeling (MESm) shifted to a higher strain-level (Figure 1). This suggests that in estrogen deficient patients exercise is even less effective than in estrogen replete patients, and that it is unlikely that

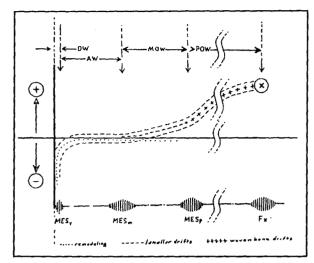


Figure 1
Model on bone adaptation to
mechanical usage proposed by
H.M. Frost: The intensity of
exercise required to shift a person
from the lower portion of the
adapted window (AW) into the
mild overload window (MOW) by
the use of exercise is considerable
especially if estrogen deficiency
shifts the threshold for the minimal
effective strain for modeling
(MESm) to a higher level.

these fragile patients could endure the vigorous exercise required to turn modeling drifts on. Ample evidence of the relative inefficiency of exercise in aging estrogen deficient populations can be found in the literature [7, 22, 3].

It is obvious that this dilemma begs the question whether it would not be possible to find agents which could lower the modeling threshold back into the normal or possibly below the normal range [13]. Such agents in combination with exercise would be able to induce modeling drifts and suppress remodeling resulting in bone gain.

A number of observations made in the past in connection with parathyroid hormone (PTH) in rats suggest, that the hormone indeed fulfills a crucial function as a modulator of the strain threshold for modeling, and that it influences skeletal maintenance. Our experimental observations looking at time and dose dependence of bone formation by pQCT (peripheral quantitative computed tomography) indicate, that bone mass and strength stabilize at a certain level which is typical for each dose administered ( [12] Figure 2).

Direct measurements of the mineral apposition rate using a multiple fluorochrome labeling protocol indicate that, coinciding with the achievement of the plateau (Figure 2), bone formation rates slowly return to the baseline value despite continuous treatment with hPTH(1-34) [12].

Such a behavior is consistent with the notion that PTH is lowering the modeling threshold (MESm) in a dose-dependent fashion, which results in the perception of a non-existing 'overload' situation (MOW) at the level of the strain sensor. PTH then increases bone stiffness by adding cortical bone through the activation of modeling drifts, until actual tissue strain levels fall again into to comfort zone (AW), correcting the wrongly perceived overload situation. Indeed, in vertebral bodies and long bones, bone strength under PTH-treatment can achieve values greatly exceeding 'normal' bone strength [16, 17, 18]. On a tissue level, the measured 50 to 100% increase in bone strength results in an 'underuse' situation (decrease in tissue strain), comparable to an 'partial disuse' situation (DW). Under normal circumstances, the proposed strain

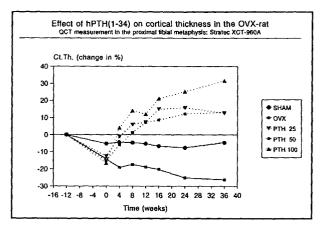


Figure 2
Measurement of changes in cortical thickness by pQCT in the proximal tibial metaphysis of old retired breeder rats treated with different doses of hPTH(1-34). Cortical thickness reaches a plateau at a value which is dependent on the dose administered.

sensor in bone will perceive this situation of relative disuse and inevitably initiate the processes required to adjust bone mass to a lower level through the activation of remodeling based bone loss. PTH is obviously capable of inducing and maintaining a situation of abnormally low tissue strain levels (abnormally high stiffness) by suppressing the adaptive response that would be expected to remove bone and normalize tissue strain levels back into the comfort zone. This tolerance of abnormally high bone stiffness without any apparent intervention to remove extra bone tissue suggests that the situation is perceived as normal by the bone mechanostat as long as PTH is administered. Again this would fit the hypothesis that PTH is capable of lowering the minimal effective threshold for induction of modeling (MESm).

Further in support of such a hypothesis, PTH and exercise were recently demonstrated to act synergistically to increase bone mass in rats [4]. The same authors also investigated the relationship between PTH and mechanical stimulation in mechanically induced osteogenesis [5]. In 'normal' rats, mechanical stimulation of the eight caudal vertebra induced an osteogenic response. This was augmented by a single injection of human PTH-(1-34) 30-45 min before loading. No osteogenic response was seen in thyroparathyroidectomized (TPTX) rats but the osteogenic response was restored by a single injection of PTH before mechanical stimulation, suggesting that physiological levels of PTH are necessary for the mechanical responsiveness of bone. cfos expression was detected only in the osteocytes of those rats that were both mechanically stimulated and given PTH. The authors took this information as a suggestion that PTH supported mechanically induced osteogenesis by sensitizing either the strain-sensing mechanism itself or early responses of bone to strain-generated signals. The osteogenic response was not augmented by two further daily injections of PTH and was not seen in TPTX rats in which PTH administration was started 3 days after loading. In agreement with our own observations these results revealed a major regulatory role for PTH in the mechanical responsiveness of rat bone.

Recent findings also indicate that PTH is a regulator of functional coupling of cell to cell communication in gap-junctions (connexin-43) of a transformed osteoblastic cell line and primary osteoblasts [20, 6]. PTH is capable to induce message traffic similar to a strain signal resulting in the activation of a glutamate transporter. Glutamate could therefore serve as a mechanotransmitter for message traffic in osteocytic networks

which due to its small size (<1 kD) is able to pass through gap-junctions. Direct evidence in support of such a function of the glutamate transporter is however still missing.

Further elucidation of strain/PTH activated signaling pathways could lead to the discovery of new valuable targets in the search for bone forming agents which act directly on the mechanosensor in bone. The use of such agents which by definition should be capable of increasing the sensitivity of the strain sensing mechanism to mechanical usage, are expected to be of particular value in combination with exercise regimens.

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