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PERSPECTIVES

Regulation of Bone Mass: Local Control or Systemic Influence or Both?

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Abstract

Bone mass and architecture are primarily of importance in relation to load-bearing. Despite this it is common to ascribe the role of "regulator of bone mass" to practically any substance that influences bone cell activity. Here we argue that "regulation" of bone mass and architecture, as a process to achieve particular local structural objectives, should be distinguished from "influence" arising from effects on (re)modeling derived from local, systemic or centrally-derived factors that are uninfluenced (often uninfluencible) by the architectural outcome. The mechanisms involved in structural regulation of bone mass and architecture in relation to functional loading are commonly termed the "mechanostat." Its controlling input is assumed to be the mechanical strains engendered within the tissue by customary loading. Even in its initial stages during which strains are transduced into biochemical responses the mechanostat does not appear to employ a unique signaling pathway; instead it shares a number of pathways used by local or systemic influences that have no feedback directly related to any particular bone mass or architecture. Through the effect of these interactions the initial assessment of strain, as well as the early responses to it, are sensitive to context. The effect of different contexts such as high or low estrogen or PTH can diminish, complement or synergize with the consequences of strain-related stimulation. At extreme levels the effect of context may mask the consequences of strain completely. Strategies for therapeutic intervention to achieve structurally beneficial effects on bone (re)modeling should therefore be designed to synergize, rather than to compete, with the mechanisms of the mechanostat. *IBMS BoneKEy*. 2009 June;6(6):218-226.

Introduction

In the 1960s it seemed, to a young investigator at least, that everyone accepted that bone mass (and by association bone architecture) were controlled by those great mediators of mineral metabolism, the calcium-regulating hormones. Furthermore, since osteoporosis was characterized principally by bone loss, the most relevant cell to understand was the osteoclast. Thus the prevailing wisdom was that the secret to preventing or treating osteoporosis would emerge from understanding the intricacies of the osteoclast lineage, the mechanisms of osteoclast action, and the responses of osteoclasts to circulating hormones. This mindset ignored the significant question of how these hormones, primarily controlled by feedback from circulating calcium, could influence bone (re)modeling to relate the mass and architecture of each region of each bone to its local load-bearing.

Harold Frost's suggestion (1) that bone mass and architecture were controlled locally by the responses of resident bone cells to the local mechanical strain in the tissue they produced was as logical as it was, in general, ignored. The reasons for this lack of attention included the scientific momentum, clinical potential and commercial opportunities behind the endocrinological approach, combined with the difficulties involved in investigating the mechanisms by which mechanical strain could influence the cells exposed to it to control the modeling and remodeling by which bones' structurally appropriate mass and architecture at each location are achieved and maintained.

Despite the sustained efforts of a small band of investigators, the mechanical influence on bone architecture remains a minority interest in bone biology (2-6). However, it was pushed towards the mainstream by a number of papers (7-14) that implicated bone cells' potential responses to strain with the high and low bone mass phenotypes associated with gain- and loss-of-function mutations of low-density lipoprotein receptor-related protein 5 (Lrp5). The realization that local strain in bone tissue down-regulated the production by osteocytes of the Lrp5 ligand sclerostin (15;16) was consistent with strain regulating bone mass and architecture through sclerostin-mediated inhibition of the Wnt pathway. In this scenario the high bone mass associated with mutation of Lrp5 is achieved by a lack of strain-related modulation of the activity of the Wnt pathway because sclerostin does not bind to the mutated Lrp5. This is consistent with the high bone mass phenotype of animals deficient in sclerostin (17). The low bone mass phenotype of animals lacking the Lrp5 gene, and thus by analogy humans with osteoporosis pseudoglioma (OPPG), could be explained by constitutive lack of activity of the Wnt pathway due to absence of one of the receptors to which Wnt can bind (18;19).

The hypothesis that the low bone mass phenotypes associated with mutations of Lrp5 are the result of Lrp5's role in mechanically-related control of bone architecture, or any other local mechanism, has recently been challenged by a powerful article by Gerard Karsenty and his co-workers (20) insightfully reviewed by Roland Baron (21). Yadav *et al*. (20) present findings showing that "Lrp5 regulates vertebral trabecular bone mass by inhibiting duodenal synthesis of serotonin, a hormone decreasing bone formation." These workers conclude that "this study uncovers an unanticipated molecular mechanism accounting for the Lrp5 *regulation* of bone formation; our findings shift the emphasis from a paracrine to an endocrine *regulation* of bone mass, and from bone cells to enterchromaffin cells of the gut" (our italics).

The paper from Yadav *et al*. (20) is an experimental tour de force showing that (in mice vertebrae at least) the differences in bone mass associated with Lrp5 mutations can be accounted for by differences in serotonin levels without having to invoke local perturbation of resident bone cells' behavior, including their adaptive responses to mechanical strain. It would, however, be over-interpretation to take this example of a systemic effect having a substantial influence on bone (re)modeling as evidence against local mechanical regulation of bone mass in more normal circumstances.

Local Versus Systemic Effects on Bone (Re)modeling

That circulating factors should have a profound effect on bone mass is not unexpected. Indeed, as mentioned earlier, this used to be the conventional wisdom as to how bone remodeling was regulated. However, this pan-skeletal influence of the hormonal milieu should not be confused with local homeostatic control or regulation in anything like the purposeful way that Frost envisaged for strain, or indeed the tight homeostatic control of processes in which hormones are the primary regulators. Frost's concept was that the strain engendered locally in bone tissue by functional loading provided a stimulus to bone (re)modeling in a feedback loop whose outcome was local control of strain (Fig. 1). Frost called his feedback loop the mechanostat (1).

It is always dangerous to ascribe purpose to biological processes since we are only ever in possession of a fraction of the relevant facts by which they operate, and the influences under which they evolved. However, it seems clear that the mass (and architecture) of bones are influenced by their strain history and that in general this relationship makes biological sense (22). Exposure to increased strain-related stimulation due to high strains, high strain rates and unusual strain distributions results in increased bone mass and/or an apparently increased strain-resistant architecture (2;4). Conversely, decreased strain-related stimulation associated with disuse results in loss of bone tissue until a

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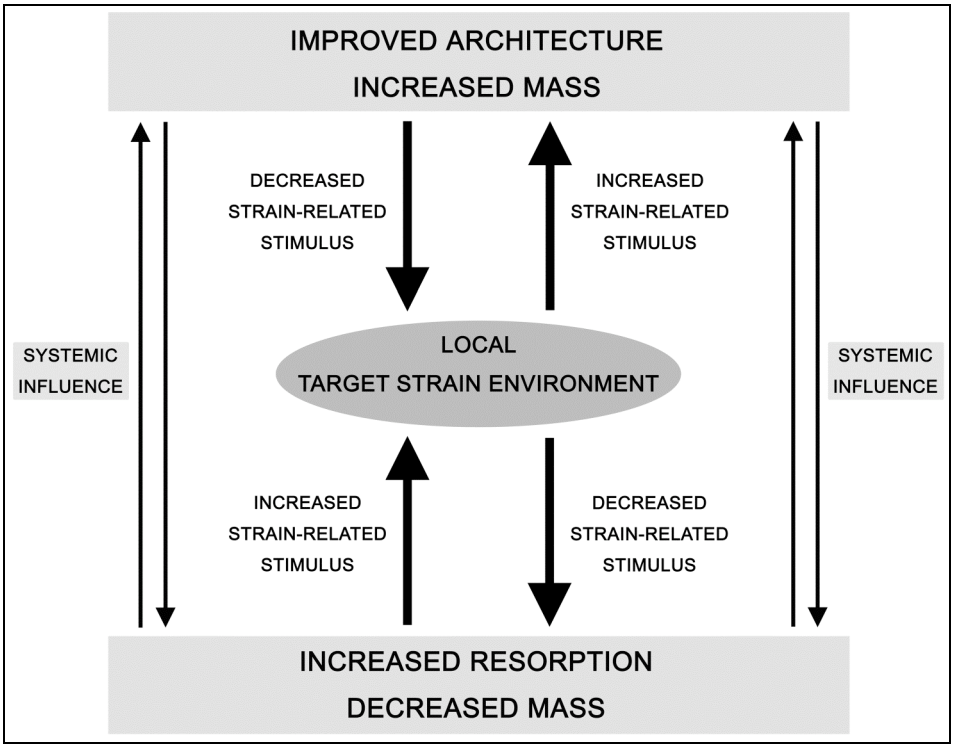

Fig. 1. Schematic representation of the feedback mechanism (the mechanostat) by which bone (re)modeling is stimulated by the discrepancy between actual and target strains to modify bone mass and architecture to regulate the strains that functional loading engenders in bone tissue. This local "regulation" should be distinguished from "influence" arising from the uncoordinated effects on (re)modeling derived from systemic factors.

baseline mass and architecture are achieved. In each case the result of the increased or decreased bone mass tends to re-establish pre-existing, target strain levels (Fig. 1).

Although our knowledge is increasing (2-4;13;15), the mechanisms by which mechanical strain is transduced into biological signals capable of influencing the bone modeling and remodeling necessary to achieve and maintain any particular mass and architecture in such a purposeful fashion are far from clear. However, as yet it does not seem as though there is a unique cellular pathway linking strain to (re)modeling. Instead, when resident bone cells are exposed to dynamic strain the activity of a number of pathways within them is altered. Thus the initial assessment of strain, as well as the early post-transduction events by which this response is processed into a signal for (re)modeling, are all likely to be sensitive to context.

Since most, if not all, of bone cells' early strain-sensitive pathways are also involved in their responses to other, non-mechanical influences, strain-related effects compete with, and complement, non-strain-related effects in resident bone cells to produce an "outcome" stimulus that regulates their own behavior and lifespan, and stimulates the recruitment and directs the activity of the cells actually responsible for modeling and remodeling (23;24). One example of strain and hormones competing for a remodeling outcome occurs when loading protects the bones involved from the resorption that would otherwise accompany systemically mediated demands for calcium (25) (Fig. 2). An example of local and hormonal influences acting to complement one another could be when intermittent treatment with parathyroid hormone reduces the threshold at which strain stimulates new bone formation (26) (Fig. 3).

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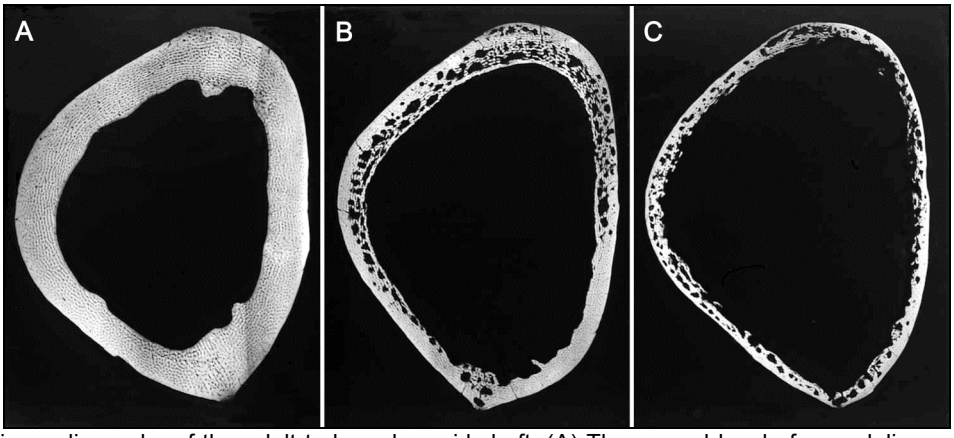

Fig. 2. Microradiographs of the adult turkey ulna mid-shaft. (A) The normal level of remodeling activity. (B) Substantial cortical thinning, endosteal resorption, subendosteal cavitation, and intra-cortical resorption due to functional isolation and calcium insufficiency induced by egg laying on a calcium-deficient diet. This bone was subjected to short daily periods of artificial loading. (C) More pronounced bone loss in a similarly functionally isolated bone, subjected to similar calcium insufficiency, that was not subjected to artificial loading. Adapted from (25), with permission from Springer.

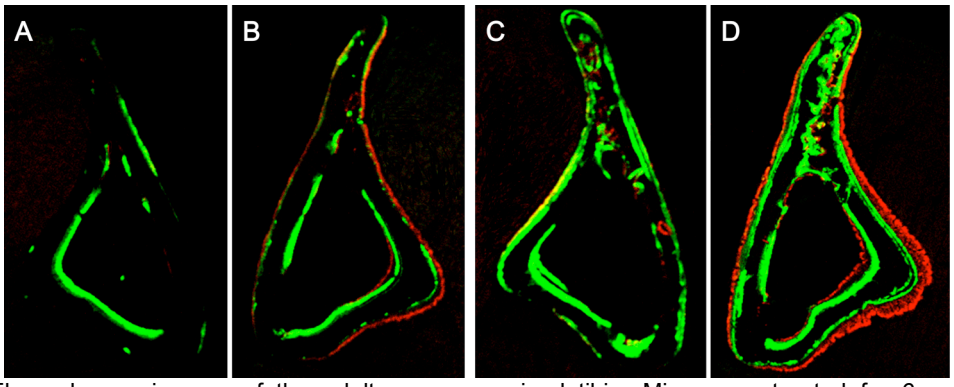

Fig. 3. Fluorochrome images of the adult mouse proximal tibia. Mice were treated for 6 weeks with intermittent parathyroid hormone (iPTH) or vehicle and during the last 2 weeks the right tibiae were subjected to short periods of mechanical loading. (A) Left non-loaded bone treated with vehicle. (B) Right loaded bone treated with vehicle. (C) Left non-loaded bone treated with iPTH. (D) Right loaded bone treated with iPTH. Green: calcein labels injected on the first day of iPTH treatment and on the first day of mechanical loading. Red: alizarin label injected on the last day of mechanical loading. Adapted from (26), with permission from Elsevier.

Limitations of the Mechanostat

One widespread example of a hormone affecting bone mass in a context-dependent manner is that of estrogen. This hormone has variable effects on the accrual of bone mass during growth and adolescence but after maturity it appears to act in a similar way to mechanical loading in preventing apoptosis of osteocytes and osteoblasts and preserving bone mass (27;28). When either estrogen or loading are removed, the balance of remodeling shifts in favor of resorption, the number of remodeling units is increased, and each event results in less bone being deposited than was resorbed. The result in both cases is bone loss. So similar are the anatomy of bone loss associated with disuse, and that associated with reduced ovarian function, that it is possible to postulate that they are both the consequence of a similar stimulus (or lack thereof) upstream of the “outcome” command for (re)modeling (29). We and others have established that the estrogen receptor (ER) is an important modifier of bone cells' early responses to strain (12;30-32). Bone cells have sufficiently few ERs

that we have hypothesized that if this number is reduced by declining estrogen levels there may be too few of them to contribute adequately to the stimulatory cascade derived from exposure to mechanical strain. An inadequately processed strain-related stimulus is equivalent downstream to one that is reduced or absent, as in disuse. The appropriate response to such a reduction in this stimulus would be bone loss regardless of whether the stimulus was reduced by inadequate exposure to strain or inadequate processing of the strain-related stimulus. Whether or not such a series of events makes a major contribution to the etiology of post-menopausal bone loss remains to be substantiated.

The wider questions are i) how do the mechanisms of the mechanostat, whose purpose is to adjust bone mass and architecture in order to achieve particular levels of functional strain, interact with the effects on bone mass of circulating factors uninfluenced, and uninfluencible, by bone strain and ii) in each individual, what actually determines the set-point for appropriate bone mass?

In the example of estrogen it is easy to envision possible mechanisms for interaction between mechanically and non-mechanically-derived stimuli since the machinery involved in processing the hormone (the ER) also participates in processing the early consequences of strain. Commonality in the tools used to produce a response leads inevitably to interaction, one consequence of which could be establishing new levels of strain-related (re)modeling responses (*i.e.*, new set points).

Interaction arising from common pathways might be expected to produce a different result from that produced if the pathways were separate. If chronically high levels of a circulating substance result in high levels of resorption and thus low levels of bone mass functional strains will be high. Does the mechanically-derived stimulus still have an effect, in this case a modifying one, even when its influence is overwhelmed? Our data (25) (Fig. 2) suggests that in some instances this may be the case.

Conversely, if bone mass were to be increased by direct stimulation of osteoblasts to the extent that functional strains were so low that they did not stimulate mechanically-sensitive pathways, then the result in terms of the strength of the strain-related stimulus for (re)modeling would be indistinguishable from that arising from disuse. However, bone mass would be high. In the absence of any osteoregulatory stimulus arising from strain, what then determines what bone mass should be? Is bone architecture still influenced to achieve structural suitability but with a radically different “set point” or is bone mass in this situation the incidental, cumulative by-product of circulating influences on bone formation and resorption?

In the analogy of the mechanostat the cooling unit of a refrigerator can only maintain the refrigerator’s temperature at the low level required if the challenge from the ambient temperature is within a certain range. If the door is left open, the workings of the mechanostat will have little or no discernible effect on the final temperature achieved. The serotonin levels documented in Karsenty’s paper (20) may be the open refrigerator door influencing bone mass through a direct effect on osteoblasts to such an extent that any influence from mechanically-related control processes is overwhelmed. However, just because it is possible to have situations where the mechanostat appears ineffective does not mean that under normal situations, in the vast majority of cases, the mechanostat is not the effective homeostatic strain-related controller/regulator of bone mass and architecture with other influences providing the enabling/modifying environment/context in which it operates.

Although we have posed questions distinguishing “control” from “influence” in terms of circulating hormones, similar arguments can be made in relation to the recent interest in “control” of bone mass emanating from the central nervous system. It seems fanciful to suggest that each area

of each bone receives sufficient efferent and afferent nerve fibers that local osteoblast activity could be directly controlled from the brain to produce a structurally appropriate, strain-related, architecture. However, it is becoming clear that the skeleton contributes to whole body homeostasis through more systems than just regulation of calcium (33-35). That these control processes should be influenced by some of the consequences of sympathetic tone should not be surprising. However, this in no way detracts from our central argument that there is no evidence that these processes are themselves directed towards purposeful control of bone mass and architecture rather than contributing to the context in which this is achieved.

Influence or Control?

That bone loading has a controlling influence on bone architecture is one of the oldest structure-function relationships to be recognized in modern biology (36). It is a relationship most evident and first recognized in the arrangement of trabeculae in relation to loading direction. It is here that the difference between systemically or centrally derived “influence” and local “control” is most easily distinguished. It is difficult to envisage how such a distributed series of local phenomena as the orientation of individual trabeculae could be controlled in any purposeful manner by circulating hormones produced at remote locations by groups of cells uninfluenced by the outcome of this aspect of their activity. Control requires relevant feedback. It is possible to envisage remote cells producing circulating factors in response to feedback relevant to the total mass of bone in the skeleton, or its surface area, but probably not such critical features as the orientation of trabeculae far, far away.

The distinction between influence and control (familiar to every parent) has implications for devising therapy as well as understanding etiology. Clearly the most desirable therapeutic objective is to establish, maintain or if necessary stimulate effective mechanically-related control of bone architecture. This would ensure that bones’ mass and architecture are matched to their functional loading, and that the incidence of fracture is maintained at normal levels, which have presumably evolved by natural selection to balance the advantages of economy with the risks of fracture. This is the situation for a large part of the lives of the vast majority of people. To some extent osteopenia, and its associated high fracture incidence, is by definition either an intrinsic failure of the natural mechanostat, or the result of circumstances by which it is inhibited, disabled or overwhelmed. High bone mass is a similar failure of the mechanostat but since it brings limited complications and is associated with decreased fragility it is a cause of less concern.

Deciding whether the origins of failure to match bone architecture to bone loading reside within the mechanisms of the mechanostat or outside them is relevant for deciding how to approach a remedy. Anything that contributes to the more effective (usually more osteogenic) workings of the mechanostat carries the possibility of influencing strategic placement of bone tissue to control functional strains. The synergy between the effects of strain and intermittent parathyroid hormone (26) (Fig. 3) supports some commonality in the way in which the two stimuli are processed. This may partly explain why intermittent treatment with parathyroid hormone is so effective at reducing the risk of fracture (37;38). Treatment that does not have this capability may be working against rather than with the mechanisms of the mechanostat and may thus be less structurally discriminating and so less effective in its outcome. Even if the therapy is working in the same generally anabolic direction as the desired mechanical stimulation, it will be less effective if its effects do not engage the advantages of acting synergistically with mechanically-derived stimuli.

In trying to devise rational therapies for achieving or maintaining structurally appropriate bone mass and architecture, we need to harness every helpful influence available. If we accept that there are specific

mechanisms whose purpose appears to be control of bone mass and architecture in relation to functional loading, then the most sensible approach to maintaining or increasing bone mass would be to amplify those pathways that already carry with them the potential to beneficially influence structural suitability. If we accept that the best therapies are likely to arise from synergy with the mechanostat, is it not now appropriate to study its mechanisms with the same enthusiasm as, forty years ago, was devoted to endocrinology and osteoclasts?

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