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Perspective Article

Hylonome

Hormonal influences on the muscle-bone feedback system: A perspective

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Abstract

Hormones, muscle and bone tissues have co-existed virtually during the whole evolution of vertebrates, and it is obvious that they constitute a complex system able to cope with needs and challenges arising from a variety of physiological and locomotive needs. All body movements are produced by co-ordinated contractions of skeletal muscles, while consequent dynamic muscle work provides the fundamental source of mechanical loading to the skeleton. Mechanical competence of the skeleton is principally maintained by a mechanosensory feedback system that senses the loading-induced deformations within the bones and maintains the skeletal rigidity through structural adaptation. In contrast to the prevalent view suggesting a modulatory effect of hormones on the sensitivity of the mechanosensory system, a new conceptual scheme is proposed. In particular, it is argued that the mechanical and hormonal functions in the skeleton are fundamentally independent but can be seemingly interactive through hormonally-induced modifications in the bone structure, those basically forming a mineral reservoir for maintenance of physiological homeostasis. Whenever needed, utilization of this strategically placed reservoir would not essentially compromise the mechanical competence and locomotive capability of the skeleton. Although plausible, the present view is necessarily speculative and awaits corroborative experimental evidence.

Keywords: Bone Mineral, Bone Structure, Estrogen, Evolution, Mechanical Loading, Osteoporosis

Introduction

The muscle-bone feedback system undoubtedly pertains to a complex mechano-biological system that primarily enables efficient locomotion but is also involved in other vital physiological functions. It is quite clear that the behaviour of such a complex system is qualitatively and quantitatively different from what can be inferred from observations and phenomena in isolated units of the whole system[1], e.g., in *in vitro* experiments based on cell cultures or molecules only. Many of the purported associations and relationships observed between macroscopic and microscopic properties may have just been consequences of choices on what particular microscopic features were evaluated against what macroscopic features. The scientific value of these approaches is by no means depreciated, but it is highly likely that the principal laws of the bone-muscle interplay at the macroscopic (whole body) level cannot be precisely, if at all, exposed by digging deeper into the microscopic details – down to cellular, molecular or genetic level.

Rather, the whole musculoskeletal apparatus should be seen and treated as a "cost-efficient" product of evolution which integrates several vital functions, along with its primary locomotive purpose, into a single organ and fills the bill – at least during the reproductive phase of life and somewhat beyond that[2]. This perspective is intended to give a reasonable picture of the locomotive skeleton and its other vital functions and particularly to capture factors that are relevant in understanding the mechanical and physiological functioning of the musculoskeletal system as a whole.

Evolutionary and environmental scope

Principal hormones, muscle and bone tissues have co-existed virtually from the very beginning of the evolution of present forms of complex life[3-7]. Given the abundance of time, some

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500 million years, it is obvious that these three physiological modules have embodied in such a universal biological protocol that is fit and efficient for virtually all foreseen locomotive and physiological demands that may occur in various forms of life. The skeleton is a beautiful example of this evolutionary process as it provides the body not only with a practical locomotive apparatus and protection of internal organs, but also with a reservoir for minerals needed for physiological functions – several vital functions integrated within a single organ!

Phylogeny and associated locomotive and loading factors basically determine the specific functional organization and features of the skeleton and musculature. All body movements are produced by co-ordinated contractions of skeletal muscles, while the concomitant dynamic muscle work provides the fundamental source of mechanical loading to the skeleton. During locomotion and other movements, the magnitude of body-weight induced reaction forces is usually multiplied due to moment arms of the musculoskeleton, rendering underlying net muscle forces relatively high – multiples of body weight[8]. In order to survive, the musculoskeleton must thus be able to adapt itself to altered loading environments by adjusting specific characteristics of its functional modules (bone and muscle) in concordance with each other. Accordingly, the apparent goal of the mechanosensory control system is i) to maintain the mechanical competence of the skeleton in terms of the predominant loading environment and ii) to keep the loading-induced deformations well below a specific safety margin in order to avoid failure. It is recalled here that the load-induced deformations arising from different dynamic locomotive activities tend to remain within a specific range within and between species[8], indicating a ubiquitous protocol for bone adaptation to prevalent loading.

The relationship between bone characteristics and mechanical loading, and particularly the underlying control system equipped with an elegant ability to sense loading-induced mechanical deformations (strains) within the affected bone structure, have been reviewed recently[9-13]. Conceptual differences, e.g., regarding the characterization of the load-induced strains (magnitude, rate, and distribution) are obvious in these approaches but some features are common. Without going into details, the common and basic principle of these approaches is that bone cells located within the mineralized bone matrix (evidently through the interconnected osteocyte network[14]) somehow sense the mechanical forces arising from locomotion (or other movements) and convert a part of the incident mechanical energy into biochemical energy (a part of this energy is dissipated into heat), which eventually results in synthesis of new bone tissue. Reduced loading, in turn, leads to removal of bone tissue from unloaded regions. Particularly noteworthy is that the sensitivity of bone response to loading is claimed to be directly modifiable by external factors (e.g., hormones) that could alter the *set-point*[a] of the mechanosensory feedback system. Details of the mechanosensory system and associated pathways from mechanical stimulus to formation or resorption of bone are sophisticated and not yet fully established[15], and are beyond the scope of this perspective.

Given the principal role of calcium[6,7], the major constituent of bone mineral (in the form of crystalline calcium hydroxyapatite), in several cellular and biological processes and functions (e.g., contraction of muscle tissue, gastrointestinal and renal functions, reproduction), the mineral metabolism within a complex organism is rigorously controlled by several parallel and partly complementary physiological feedback systems involving intertwined hormonal functions. Failure in the regulation of calcium metabolism would be lethal and the need for redundant systems for adequate safeguard and backup functions is self-evident. Consequently, many hormones (primarily 1,25-dihydroxycholecalciferol, parathormone and calcitonin) are concerned with the regulation of calcium metabolism. In addition to these three hormones affecting calcium metabolism and bone formation and resorption, adrenal glucocorticoids, growth hormone and insulin-like growth factors, thyroid hormones and estrogens are involved and interacting through several feedback systems securing the physiological homeostasis.

Hormones act through and are regulated by a system of specific receptors and binding proteins[16]. Genes, in turn, encode for nucleid acids and subsequent proteins that carry out the reactions in living systems and control concomitant physiological functions. Under normal circumstances (potential mutations and related peculiarities excluded), the genetic control of vital functions is pleiotropic (one gene is linked to a variety of functions or phenotypes) and multigenic (several genes are linked to a specific function or phenotype), again most likely for apparent safety reasons. Of the above mentioned arsenal of hormones, estrogen has probably received the most attention, which is not surprising given its essential role as a primary cause of postmenopausal osteoporosis[17]. In many studies, estrogen has also been suggested to be a central modulator of skeletal response to loading, but the interpretations and conclusions are not consistent[18-22], and this topic has aroused a lot of debate[23-27].

Distinction between mechanical and hormonal influence

In this perspective, a conceptually novel scheme for bone-muscle interplay is presented. The new approach fully agrees with the previous schemes in that the bone has the ability to

[a] In the present context, the set-point should not be strictly considered a fixed threshold representing a specified magnitude of deformation (e.g., in microstrains) above which the incident deformations will result in increased bone rigidity and below which decreased bone rigidity will follow. In fact, the set point denotes a relatively wide physiological range of deformations within which the incident deformations would not lead to substantial skeletal adaptation in either direction, if any. It is also stressed that the set-point pertains to dynamic loading situations, when not only the strain magnitude, but also the strain rate play an essential role.

sense loading induced deformations (without paying attention to details of underlying mechanisms or the specific nature of deformations) and to adapt its structure reasonably to an altered loading environment whenever needed, but essentially disagrees in that the humoral factors (e.g., hormones) do not *directly* modify the sensitivity of the load-sensing mechanism. It is particularly argued that there is principally no need for such a complicated adjustment of the set-point, meaning that an aberrant set-point does not exist in the mechanosensory control system. It is proposed that both the mechanical and hormonal functions can be solved in a straightforward manner without compromising the performance of the musculoskeleton or violating existing clinical or experimental observations.

The seminal observations by Schiessl et al.[23] and Ferretti et al.[28] provide relevant cornerstones to this new proposition. The former group, using the data readily available in the literature, incisively exposed that the amount of bone mineral (bone mass) in relation to muscle mass in post-menarche (estrogen-replete) girls and women appears to be clearly higher compared to boys and men[23]. The latter group further showed that this excess bone mass seems to disappear after menopause, indicating that the ratio of bone mass to muscle mass in estrogen-deplete women returns back to the level in men of similar age. We revived this paramount idea in our recent perspective concerning the role of the skeleton in reproductive and locomotive functions[27].

If we assume that bone mass and lean body mass are reasonable surrogates for skeletal rigidity and mechanical loading arising from muscle activity, respectively, the above *in vivo* macroscopic observations can be interpreted by two seemingly plausible but mutually exclusive ways. First, one can argue that estrogen sensitizes the mechanosensory system to loading[9,10,13] (i.e., compared to an estrogen-deplete situation, smaller loading-induced deformations would be sufficient to initiate bone formation in estrogen-replete situations). Customary loading would thus result in greater bone mass. Conversely, withdrawal of estrogen (due to menopause or amenorrhea) reduces the sensitivity to loading and leads to bone loss, as the concurrent loading is not sufficient to counter this change in mechanosensitivity. The alternative view is that at puberty the rise in estrogen levels simply leads to the deposition of additional bone mass to satisfy the anticipated physiological needs of the subsequent reproductive period[27]. At menopause, this ~20% surplus of bone mineral (compared to men) is removed as unnecessary, which becomes manifest as postmenopausal bone loss. While both views provide an equally plausible explanation for the observations, the latter interpretation constitutes a simpler solution and does not require a mechanism that could alter the sensitivity of the mechanosensory feedback system. The new scheme is entirely based on the latter interpretation.

Given the evident causal link between muscle activity-induced loading and bone characteristics[9-13], maintenance of the mechanical competence of the whole functional organ (musculoskeletal system) through structural adaptation remains the major, and most likely, the one and only goal of the mechanosensory system. In this context, it may be useful to dispel a common misconception regarding the bone mass and bone mechanical competence. Despite the fact that the correlation between bone mass and whole bone strength can be very high (r up to 0.9 or more), this strong association does not imply that the bone mass as such equates with the mechanical competence of a bone. Bone mass simply reflects the amount of material of which the bone structure is made, but does not convey any specific information of how reasonably, in mechanical terms, the bone mass is spatially distributed within the bone volume. It is ultimately the bone structure, characterized by overall size and geometry, cortical geometry, thickness and porosity, internal trabecular architecture and organisation, that determines whole bone mechanical competence (structural rigidity or stiffness, and strength) in different loading environments - provided that the material properties are not substantially compromised[2,29].

The hormonal control of physiological homeostasis of the body, in contrast, is only concerned with the access to readily interchangeable reservoir of minerals (bone mass) that may be required; e.g., during pregnancy and lactation, nutritional deficiencies, starvation, or diseases - while not critically jeopardizing the mechanical competence of the skeleton and consequent locomotive capability. As there is probably no feedback loop that would inform any endocrine system about bone structure and its rigidity, the latter condition requires that the bone elements representing the mineral reservoir are not critically located in terms of mechanical competence. This means that the excess bone should be placed on the endosteal surface of cortical bone and on the surfaces of trabecular bone – next to the bone marrow. And indeed, premenopausal (estrogen-replete) women are known to have more cortical bone in relation to bone cross-sectional area, higher cortical density, as well as higher trabecular density at some sites, compared to men[30-33]. This difference is also evident between pre- and postmenarcheal girls[34], between pre- and postmenopausal women[35], and also between those postmenopausal women who are on estrogen replacement therapy or not[36]. From a mechanical point of view, it is recalled here that even endocortical thickening of a cortex, without a change in external diameter, makes the bone structure stiffer – although not as much as periosteal expansion does[37]. A higher cortical density, too, is associated with increased stiffness of cortical bone[37].

All in all, the main skeletal targets from the viewpoint of loading (mainly induced by muscle activity) and hormones concern different features of bone. However, since these basically independent factors act on the same bone structure and affect the mechanical behaviour of the whole bone organ, some [secondary] interaction can be expected.

The new conceptual scheme

Figure 1 depicts schematically the muscle-bone feedback system with the specific feature of including separate feed-

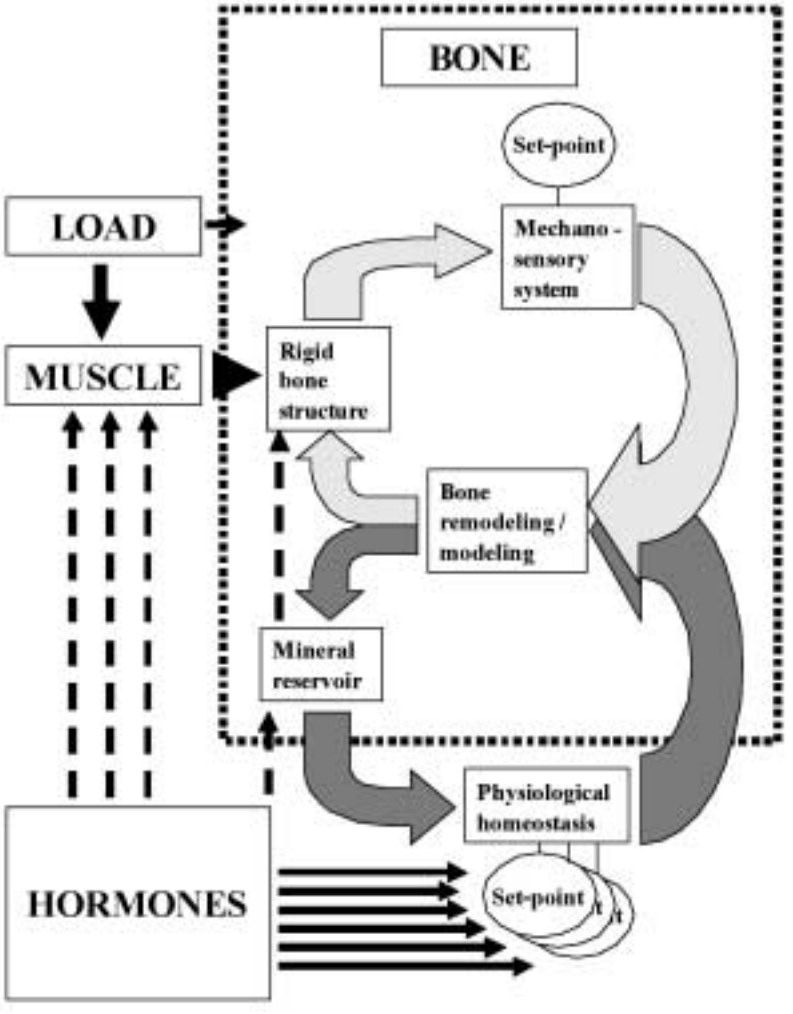

Figure 1. Schematic description of independent and separate feedback control systems for the maintenance of mechanical competence of the skeleton through structural adaptation of bones and the maintenance of physiological homeostasis of the body through employing a mineral reservoir embedded in the bone structure. During locomotion and other movements, the load is transmitted to the skeleton mainly though dynamic muscle activity. Hormones modulate the loading through affecting the growth and muscle performance and indirectly through potential changes in the mineral reservoir. See further discussion in the text.

back control systems for sensing the loading-induced mechanical deformations within the rigid bone structures and for maintaining the physiological homeostasis within the body. It should be noted that these basically independent functions share the same bone modelling-remodelling apparatus. Further, distinct from previous schemes[9,10,13], the set-point of the mechanosensory system is considered fixed (i.e., not modifiable by hormones), while the set-points of hormonally mediated control systems responsible for maintaining the physiological homeostasis can be complex and subject to potential interplay between hormones, besides being influenced by physiological conditions, health status, nutrition, age, and genetics. Hormones (e.g., testosterone, growth hormone) can also directly modulate the bone loading through affecting the muscle performance (force and power) and indirectly the deformations through the estrogen-induced mineral reservoir integrated in the bone structure. As mentioned before, many other hormones are involved in calcium metabolism of the body. Since all of these systems readily exist within the body, the actual situation is not violated.

As argued before, the loading is solely interested in an adequately rigid skeletal structure (structural rigidity is closely related to the strength of the whole bone), a pre-requisite for efficient locomotion, while hormones are solely interested in accessible bone mass (minerals) that can easily be released for physiological needs. It is recalled that the bone modelling-remodelling apparatus transforms both the mechanically or hormonally-induced chemical signals into activity of bone cells that eventually results in formation or resorption of bone tissue, as appropriate, for the specific loading or physiological condition. Specific details concerning the transformation of deformation-induced mechanical

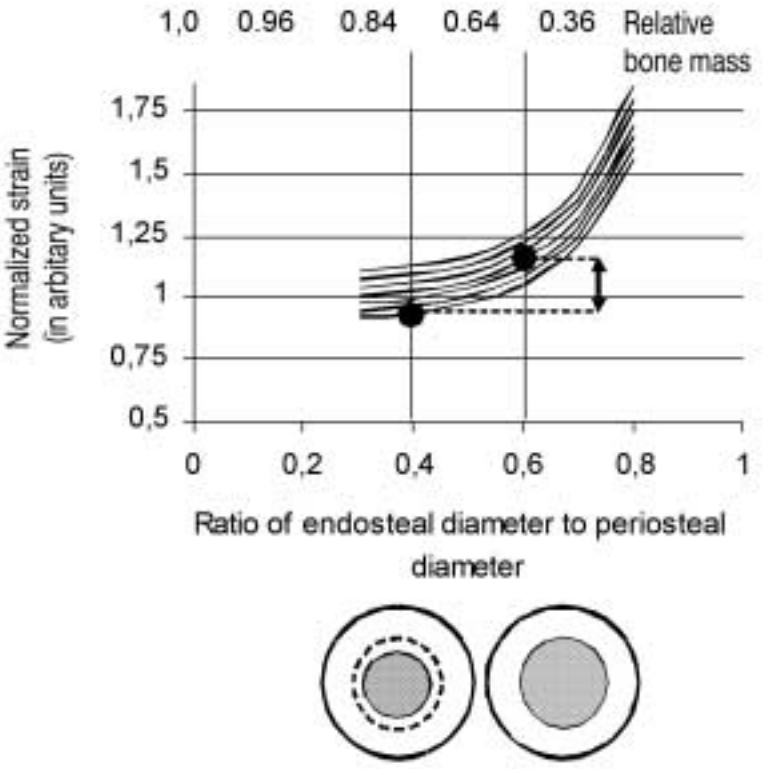

Figure 2. Theoretical relationship between maximum strain and relative cortical thickness [endosteal diameter (d)/periosteal diameter (D)] in a bone cylinder subjected to equal bending load [strain α bending moment/EZ, where E denotes the Young's modulus (material stiffness α third power of cortical density[37]) and Z the section modulus calculated according to the standard formula, $Z = \pi/32D \times (D^4 - d^4)$]. For simplicity, bending moment and cortical density were normalized to one. The strain value of one corresponds to situation when the bone cylinder is solid (no marrow cavity) and its density is one. The parallel curves show the effect of varied cortical density (±3% in 1% steps) on the relationship. See further discussion in the text.

energy into chemical signals are not relevant to underpin the new scheme.

The above noted hormonal modifications in bone structure[30-36] inevitably increase the rigidity of the given bone. This skeletal modulation, attributable to independent hormonal effect and evident not only in the relative bone mass and structure but also indirectly in the mechanical behaviour, can be fallaciously interpreted as an increased sensitivity to loading (equal load causes a more robust bone appearance) - or in line with the present view, as an independent hormonal addition of interchangeable bone mass to the endosteal surface and trabecular structure.

Figure 2 illustrates the influence of hormonal modulation on bone rigidity and strains in a simple bone cylinder. Compared to a "male-type" bone (without the estrogen effect), the structural stiffening inherent in a "female-type" bone (with the estrogen-induced relative cortical thickening at the endosteal surface and denser cortical bone tissue) decreases the magnitude of deformations at a given load. Although the deformations in the "female-type" bone are somewhat reduced, no disuse-induced bone loss would occur because the set-point of the mechanosensory system apparently represents a relatively wide physiological window[9,10]. It is naturally required that normal physical activities (e.g., walking) are performed – a complete disuse, long immobilization and declined physical performance would most likely lead to bone loss despite the hormonal influence. The removal of bone mineral from "reservoir" compartments, in turn, would only marginally affect the structural rigidity of the bone, and the consequent loading-induced deformations would not deviate from the set-point sufficiently to initiate substantial skeletal adaptation. So, in order to gain substantial skeletal adaptation, a woman would need to expose her bones to relatively higher loads than a man. As indicated in Figure 2, in order to be able to override the effect of estrogen on bone rigidity, some 20% higher loading would be needed to create deformations that would correspond to typical deformations in the "male-type" bone in a normal situation.

Fully in line with this argument, male tennis players display a twice greater average effect in side-to-side differences between the playing arm and non-playing arm than female players[38,39]. Likewise, the bone response to a similar jumping exercise is significantly higher in premenarcheal girls (without estrogen modulation) than in postmenarcheal girls[34].

The above theoretical example and clinical data demonstrate that regardless of the primary goal of estrogen to store bone mineral for potential further physiological use, the hormone-induced, indirect structural modification is also reflected to mechanical behaviour of the whole bone, and thus indirectly to its mechanical adaptability.

Conclusion

Although this perspective largely dealt with the modulatory effect of estrogen only, the following interpretations regarding the impact of other hormones on the bone-muscle feedback system cannot be ruled out. Hormones, as such, are not interested in bone structure or mechanical competence of the skeleton, but they are almost exclusively concerned in maintaining the calcium homeostasis (through bone-embedded mineral reservoir) and coping with physiological needs whenever they emerge. As an exception (that proves the rule), the axial growth of bones and its cessation is mainly modulated by growth hormone and estrogen. Otherwise, irrespective of hormonal influence, the bone would, without loading, remain quite slender in terms of axial length[40]. It is also worth noting that hormones (particularly testosterone and growth hormone) affect muscle growth and force production capacity of muscles[41-43], a fact that is most likely translated into the bone structure through concomitant loading of bones, but by no means through modulating the responsiveness of mechanosensory system. Dynamic muscle activity incontestably underlies the mechanical loading of bones, but it is solely the specific loading environment that becomes beautifully reflected in the bone structure – e.g., erect bipedal locomotion in the cortical structure of the femoral neck[44], functional features of the upper and lower extremities in the cross-sections of humerus and femur during growth[45], extreme weight-bearing loading in the structure of the tibia[46], not forgetting the apparent impact of loading on the skull[47].

In summary, the goal of the mechanosensory feedback system is solely to maintain the mechanical competence of the skeleton in terms of predominant loading environment through reasonable structural modifications as long as possible, while bone mineral residing basically in the reservoir embedded in the bone structure is occasionally or permanently accrued or removed for physiological needs in concert with incident hormonal control and status. In contrast to the prevalent view suggesting a modulatory effect of hormones on the sensitivity of mechanosensory system, it is argued here that the mechanical and hormonal modules are fundamentally independent but can be indirectly interacting through hormonally-induced modifications in the bone structure, those being mainly manifest as higher cortical density, relatively thicker cortices in terms of external diameter, and higher trabecular apparent density. The present view is naturally speculative and awaits corroborative experimental evidence.

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