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Editorial

Does the Mechanical Usage (MU) Inhibit Bone "Remodeling"?

"It is a merit of a theory to be proved false."
—Noam Chomsky

This seemingly esoteric question concerns the fundamental problem of skeletal biomechanics, namely, how the skeleton maintains its mechanical competence (MCSk), that is, its capacity to support and to endure. By the same token it concerns how various alterations in bone structure and/or materials properties might account for skeleton's mechanical failure, especially in adults.

In that context "remodeling" could denote the mechanism by which bones in adults adapt to actual mechanical demands and remain mechanically competent. At issue therefore are not the observed effects of mechanical usage (MU) on bone structure or its materials properties, but the underlying cellular mechanisms. As the question mark in the title implies, that issue discussed recently by Frost [1, 2] is not settled. In fact, the term "remodeling" itself needs to be defined.

The nature and the scope of the argument require that its background be reviewed along with a few relevant basic concepts of bone physiology as seen from this perspective. Consequently, the text is divided into four parts: Background, Mechanical Usage, Effect of MU on basic multicellular unit of lamellar bone turnover (BMU)-based lamellar bone turnover (LBT), and Concluding Inferences and Remarks.

Background

Three Processes that Make Bone

At any given time the structure of bones sums up three separate processes, of which only the last directly concerns the argument at hand. As for the first, the basic species-specific morphology, including bone architecture, evolved during phylogeny. The instructions for realizing the basic blueprint for bones during ontogenesis is encoded in the genome. Thus, bones' structure is grossly pre-adapted to patterns of mechanical loading which the anatomic relations within the locomotor system (i.e., muscle and tendon insertions, joints with their ligaments, and bone marrow within bones) impose on bones once weight bearing, and muscular exertion is assumed early during the postnatal growth.

The second process is associated with ontogeny. In embryo, the basic bone architecture (i.e. the genotype), unfolds along with the locomotor system (LMS) and it is then maintained while all anatomic elements increase rapidly in size. In the final analysis the basic architecture of bones, especially their trabecular pattern, is maintained by the intense bone turnover. Thus, while osteoblasts provide the structural material from which bones are finally made (i.e., lamellar bone), osteoclasts, by resorbing it in selective areas, contribute further to the emergence and maintenance of structural bone genotype.

The third process converts the genotype into phenotype by adjusting bone structural and materials properties. It begins to take place when the skeleton becomes subjected to its *actual* mechanical usage in the earth gravity environment [3] during both postnatal growth and in adults. This is because, in a nutshell, the same kinds of cell populations, (i.e., the osteoblasts and osteoclasts that elaborate the genotype) have the further ability to respond to signals or stimuli generated by strains when bones are subjected to mechanical loads that are significant from the point of view of MCSk. It is implied that without such adjustments in bone structure and its materials properties, the MCSk (i.e., the skeleton's capacity to support and endure its MU) would become impaired because excessive

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stresses and strains would cause microdamage to accumulate and lead to bone fragility, and eventually to fractures [1, 2].

Components of Skeleton's Mechanical Competence (MCSk)

The sequential and piecemeal character of bones assembly and of their subsequent turnover by local, self-renewing, transient osteoblast and osteoclast populations account for the three orders of bone structure as well as for its materials properties, each potentially contributing to MCSk.

Gross bone architecture, size, and mass (i.e., its gross global aspects) constitute the first order structure; the structural units of lamellar bone or BSUs [4], the outcome of local sites of bone turnover such as haversian systems, constitute the second order structure; and the arrangement of lamellae with vertically versus horizontally aligned collagen fibrils bundles, the third order structure [5, 6]. But bone growth and the rate of LBT also determine the mean bone age and related certain materials properties of bone tissue. Thus, recent and less fully mineralized tissue, by being more compliant or less stiff, develop less microdamage than older fully mineralized lamellar bone which is more likely to undergo irreversible plastic deformation when overstrained [7].

Therefore, the piecemeal manner of bones assembly and turnover has important consequences. Any change in the first order structure implies the change in second and third order structures as well as the materials properties related to the mean tissue age. On the other hand, the piecemeal LBT does not need to affect the first order structure (i.e., bones' gross architecture and/or mass). This type of LBT, which characterizes mainly the mature skeleton, is referred to as "remodeling" [8]. Clearly, how any form of LBT affects bone structure depends on the responses of the underlying cellular mechanisms to genetic (intrinsic) as well as environmental (extrinsic, including biomechanical) factors. These mechanisms, referred to as the Effector Organ of Lamellar Bone Turnover System (EO LBTS) [9], account for most of Frost's intermediate organization (IO) of bone [8].

Bone Envelopes

In this discussion bone envelopes occupy a pivotal situation. First, the genetically determined gross shape and architecture of bones are defined (modeled) by the envelopes' spatial relationships. Second, the adjustment of bone mass, which is an important component of MCSk, involves changes in the spatial relationship between the periosteal and cortical endosteal and trabecular envelopes and the LBT-determined bone balance on each. And third, the components of the LMS may specifically affect the envelopes in contact with them (Envelopes Specific Behavior) [10].

The spongy parts of the skeleton (i.e., short bones as well as the epi- and metaphyses of long bones) are encased between two envelopes: the *external* which apart from the articular surface covered by the cartilage consists of the periosteum (or perichondrium), and the *internal* (i.e., the endosteal cortical and trabecular envelope).

As to the diaphysis of long bones, because during growth bones' outer circumferences enlarge faster than the bone marrow cavity, diaphyseal cortices increase in thickness. This is associated in large, long-living animals, under normal circumstances, with the "colonization" of the external bone periphery by haversian systems, while, due to the erosion of the endosteal surface, the bone marrow invades the adjacent haversian systems, and the juxtamedullary cortices undergo trabeculation [11]. Thus, the network of Volkmann's and haversian canals carrying blood vessels communicating with the circulatory system on both the periosteal surface and within the bone marrow, could be said to form in the diaphyseal, and compacta an additional or *third envelope*.

Importantly, though the endosteal envelope is in direct contact with the bone marrow, the periosteal one is the site of muscles and tendons insertions. It is thus subjected to pulls when contracting muscles overcome the bone weight (inertia) in earth gravity environment [3].

Mature Skeleton

With the cessation of growth, while bone size and architecture (under normal circumstances) remain unchanged, the skeleton undergoes three other important changes, in part under the influence of its MU. First, the LBT form, which during growth maintained the shape and architecture (first order structure) of bones as they increase in size (i.e., *primary* bone formation and resorption drifts occurring in separate locations on periosteal and cortical endosteal envelopes) is replaced by turnover sites in which bone formation *follows* bone resorption.

Second, while the marrow cavity and periosteal

envelopes continue to enlarge, albeit at a slower rate, the marrow cavity now expands faster. The accompanying thinning and loss of trabeculae in the center of spongy parts, and trabeculation and thinning of the cortex from within account for the universal age-related bone loss [12].

Third, the bone tissue mean age progressively increases too, and with it, at least in areas of low LBT, bone tissue becomes less compliant and more susceptible to microdamage when exposed to unusually intense MU [1].

Modeling and "Remodeling"

Modeling would mean, therefore, the acquisition, during the embryonic stage and then the maintenance during growth, of the species-specific bone shape and architecture, the result of several different processes and LBT forms [9]. On the other hand, "remodeling" refers to the form of LBT that the skeleton undergoes mainly after growth stops, which is done by BMUs [10]. (Historically, the term "remodeling" was applied first to all processes that shape bones and establish their architecture [13]. In the early 1960s, Frost aptly referred to this process as "modeling" [14] and reserved the term "remodeling" for the haversian form of bone turnover which he subsequently extended to cover all sites in which bone formation follows local resorption, i.e., to such sites on the periosteal and cortical endosteal envelope after the cessation of growth [10, 14]. As in the first instance, however, it was not a fortunate choice because first, this term can signify a global reshaping of bones [15], and second, although the realignment of haversian systems particularly may be viewed as a sort of internal remodeling [16], this type of LBT as mentioned, may affect also the envelope balance or whole bone volume, and the mean bone age too. Hence, it affects not only bone's structural but also its materials properties. The term "BMU-based LBT," being descriptive and neutral, therefore appears the safest to use.) In such skeletal sites, osteoclasts recruited from progenitor cells appear first (the event referred to as activation [10]), assemble into a discrete self-renewing transient population forming the resorption front [9], and, supported by a capillary loop, resorb parallel to the bone surface a cavity a few cubic millimeters large; then a monolayer of osteoblasts also recruited from the local dividing progenitor cells, an event termed coupling [17, 18], subsequently refills the cavity perpendicularly to its bone surface. A packet of lamellae aligned parallel to that bone surface (i.e., a structural unit of lamellar bone) (BSU) [4] constitutes the outcome of a BMU moving across the bone space or surface, of which haversian systems or osteons are familiar examples.

While the evolution and form of BMUs, and hence their outcome (i.e., BSUs on various bone envelopes), may vary in their configuration, size, and balance, they all share two essential features already referred to: activation and coupling.

Activation

Activation, a bone surface phenomenon, constitutes the basic determinant of LBT in general, and BMU-based LBT in particular [19]. On the one hand, it implies the existence of intrinsic and extrinsic signals or stimuli, the latter distributed throughout bone, and on the other, the existence of corresponding genetically determined cell sensitivity and responsiveness which includes the capacity of progenitor cells to divide and differentiate into functional cells. Thus, these cells appear to possess, in addition to receptors to hormones, growth factors, cytokines, etc. [20], some sort of "mechano"-receptors. Otherwise the space-oriented and structure-producing activities of these osteoclast and osteoblast populations could not be integrated and regulated [9, 19].

The number of such activation events per unit time and bone surface and volume (i.e. the activation frequency [10]) implies that the stimuli generated by significant strains, those capable of affecting the effector cells of LBT (EO LBTS), should be more or less widely distributed and in a more or less permanent fashion in bone and on its surfaces.

Coupling

In this context, coupling means that the appearance of osteoblasts in sites of LBT is linked to osteoclasts by some related coupling factor [17, 18, 20]. In contradistinction to LBT in modeling, only *secondary* lamellar bone apposition takes place in BMU-based LBT, meaning in sites of prior bone resorption. This implies that in a mature skeleton in particular, the osteoclast progenitors are more responsive to biomechanical factors, and in general to a wider range of stimuli, then the osteoblast progenitors which would depend on some osteoclast-derived coupling factor for activation [20]. But once activated, the osteoclast and osteoblast populations exposed to prevailing biomechanical and/or other

factors should respond accordingly. Thus, while the activation of osteoclast populations is a *sine qua non* for BMU-based LBT, the subsequent rate and duration of functional osteoclasts and osteoblast recruitment from their respective progenitors, along with the life-span and the fate of the differentiated cells, will determine the individual BMU evolution, form, and outcome in terms of size, shape, and bone balance of the resulting BSUs [9, 19].

BMU-Based LBT and Envelope-Specific Behavior (ESB)

Local factors related to the anatomic relations of the envelopes may influence the BMU activation frequency and the subsequent evolution and outcome of BMUs, to account for the so-called envelope-specific behavior (ESB) [10].

Thus, the bone balance is positive within BMUs on the periosteal envelope, linking bones to the rest of the LMS, and negative on the juxtamedullary haversian and endosteal envelopes in contact with the bone marrow. The prevailing negative bone balance on the latter results basically from the mean depth of erosion (MDE) exceeding, on the whole, the mean wall thickness of lamellar bone (MWT) deposited within BMUs; on the periosteal envelope, which is subjected to biomechanical factors such as muscle pull and bending, the reverse seems to be true [10].

On the other hand, the realignment of the haversian systems, especially in the external two-thirds of the diaphyseal cortex where they are in balance (MDE = MWT), may be affected by the requirements of blood flow in compact bone [21, 22]. In its lacunar-canalicular system, the resident osteocytes depend for oxygen and nutrient supply on diffusion from the closest capillary within haversian canal [23].

Johnson reported the absence of haversian systems in bones of the congenitally paralyzed limb [24], which could imply that mechanical loads activate the haversian LBT. But since in such instances the diaphyseal cortices remain thin, this may be an indirect effect of MU, which primarily by promoting transverse bone expansion would secondarily cause the haversian systems to evolve [21, 22].

The haversian envelope also appears to be particularly sensitive to neurocirculatory factors (see RAP) and hormones, especially those implicated in calcium ion homeostasis in the body fluids. Thus, when it is challenged, as during a growth spurt in boys [25] or during rapid antler growth [26], or in general during acute negative calcium balance, the number and size of haversian cavities may increase dramatically [27].

Mechanical Usage (MU)

Effect of MU on Bone Mass

The structural adaptations to mechanical demands *during growth* would consist mainly of the accumulation of bone mass over what would be determined by the genotype. Thus, the mechanical regulation of bone mass should be grafted on the transverse bone growth mechanisms, that is, it affects the spatial relations between the periosteal and endosteal bone envelopes. Growth and physical activity, that is, weight bearing and muscular exertion (muscle pulls through muscle and tendon insertions) subject bones to a variety of strains and that seems to enhance bone apposition on the periosteal envelope and to mitigate the negative balance on the endosteal one [1, 2]. The importance of the bone mass accumulated during growth (phenotype vs. genotype) lies in the fact that after maturity under ordinary circumstances it can be maintained (i.e., the age-related bone loss can be kept in check) [28] but not greatly increased or reversed as in prepubertary girls [12]. The BMU-based LBT seem unable to generate any large global positive bone balances perhaps because of intrinsically limited MWT within BMUs [29]. However, in conjunction with realignment of second and third order structures as well as with continuing bone renewal, the LBT is able to maintain the MCSk in adults.

Thus, bone, and also muscle mass, are usually greater in those whose occupations, regular participation in sports, or general life-style imply a more intense use of the locomotor system [30–32].

Steady States and Shifts (Transients)

It is important to distinguish between steady states when bones are structurally fitted to a given level of typical physical activity (which may range from very low as in a sedentary life to very intense), and the shifts from one such level to another, which can occur rapidly or slowly. Probably because of unavoidable alternation between nocturnal rest and diurnal activities, when most significant MU takes

place as well because of sporadic variations in customary activities (and later in life because of the age-related bone loss), bones may never become fully adapted to their MU, and the BMU-based LBT may reflect that, provided the same regions of the skeleton are compared [33]. Nevertheless, the LBT in the same areas of bones structurally adapted to a given level of mechanical usage should be comparable and less active than during rapidly occurring adaptations.

Intensity Vs. Pattern of Mechanical Loading

So far, only the changes in bone mass in response to the intensity of MU within the pattern of loading (i.e., customary loads application and strains distribution) were considered, which are determined by the normal anatomic relations between the components of the growing or adult LMS. But the changing species customary LMS anatomic relations, especially in growing individuals, can alter the species normal bone architecture. Thus, a global *remodeling* may take place, involving the first, second, and third order structures, justifying the use of the term in this instance [15].

The Skeleto-Muscular Tandem

The adaptation of bone to mechanical demands obviously does not take place in isolation from the rest of the locomotor system, and particularly from muscles function. Thus, muscle contractions, apart from their mechanical effects on bones, also affect blood flow within bones and bone marrow [21, 22]. Furthermore, the muscle bulk and bone mass change is parallel [34, 35]. Aside from the adaptive mechanisms in bone which muscle action may trigger, muscles as well as the ligaments brace and stabilize joints in action as well as parts of the skeleton not in motion at a given moment (i.e., walking, running, jumping, lifting, etc.). Whereas under normal circumstances loads application results in strain distribution to which bones are already adapted, with weak muscles and ligaments unable to properly stabilize the joints, altered loading and strain patterns may increase microdamage and cause, before the repair mechanisms take over, bone fragility. In Bone Fragility Syndrome of Aging [19], therefore, the increased incidence of fractures may be due in part to the excessive microdamage production resulting from the lack of coordination within the skeleto-muscular tandem.

Effect of MU on the BMU-Based LBT in Adults

Acute Disuse Osteoporosis

Discussion of the effect of MU on the BMU-based LBT can now be approached from the perspective of what has been reviewed so far. Frost, focusing on the effect of MU on bone mass and extrapolating from acute disuse osteoporosis, inferred that MU inhibits "remodeling" (i.e., it would depress BMU activation) while at the same time mitigating the customary age-related negative bone balance [1, 2]. Indeed, a sudden complete withdrawal of mechanical loads (i.e., acute immobilization) does result in a rapid bone loss which continues until the reduced bone mass and new limited mechanical demands equilibrate [36].

However, the sequence of events studied in dogs deserves closer scrutiny [36]. At first one observes a burst of new resorption cavities on all envelopes (i.e. activation of new osteoclast populations, possibly due to Regional Acceleratory Phenomenon (RAP) [37] which tend to revert into bone-forming centers as the immobilization continues, except on the specific envelope where the protracted bone loss takes place [36]. That loss in spongy bone occurred on the endosteal envelope, but on the periosteal envelope in diaphyses in young adult dogs, and on the cortical-endosteal envelope in old dogs [36]. This loss was not due to the accentuation of negative bone balance within BMUs, but rather to the appearance of resorption drift, due to a continuous recruitment of osteoclasts in activated sites that led to extension and fusion of cavities (i.e., a marked extension of resorption surface), as well as to a failure of osteoblasts to appear in the transitional zone [38], which could be called "uncoupling." This uncoupling could represent a continuous recruitment of osteoclasts leaving no space for osteoblasts, or more likely an inhibition of the "coupling factor." The onset of a new steady state under such circumstances (i.e., the arrest of further bone loss with a permanently reduced bone mass on the other hand) begins with a fall in further osteoclast recruitment and a conversion of active resorption surfaces into inactive ones [36].

But even if the initial burst of BMU activation and the subsequent disuse-specific bone loss could be viewed as a release from inhibition exerted by MU, the inference that MU only depresses the BMU activation and inhibits "remodeling" does not necessarily follow. As Frost himself suggested, significant strains, those exceeding the threshold of the EO LBTS responsiveness or Minimum Effective Strains (MES) [39], could also result in BMU

activation. The strains below that level or "trival" ones characterizing the structurally adapted bones may, however, still keep in check factors that trigger the disuse reaction upon a *complete* withdrawal of mechanical loads. Such factors could differ from those generated by strains. Thus, the changes in LBT during acute disuse osteoporosis should be treated apart from changes taking place during upward or downward shifts in the vigor of normal physical activity, that is, when the adaptation is taking place under more or less physiological conditions. On the other hand, one can compare and contrast the LBT activity responses to a downward shift in physical activity, excluding the reaction to acute disuse and to upward shift.

What direct evidence would bear on how MU influences cellular mechanisms that achieve the bone mass effects in adults?

Remobilization Experiments

The few such reported experiments [40] show that a considerable recovery of bone loss can take place when loads are reimposed (remobilization) during the active phase of disuse osteoporosis. Such experiments reveal the cellular mechanisms of the bone mass recovery and the new steady state towards the end of the acute disuse reaction [36].

The recovery of bone during remobilization results from a decline in osteoclast recruitment and from the resumption of osteoblast recruitment and function. That rapidly converts markedly extended resorption surfaces into sites of intense bone formation [40]. Such data would suggest that the imposition of MU inhibits BMU activation and subsequent osteoclast recruitment when those are already greatly increased. But they also show that MU reestablishes coupling and enhances the recruitment and function of osteoblasts, thus allowing bone formation to "catch up," as it were, with the prior excessive resorption. One could conjecture from such evidence that during postnatal growth MU could similarly mitigate bone resorption and enhance bone formation in sites where they respectively take place, that is, add mass to the basic architecture as defined by the genotype.

Acute Overload Experiments

Few such experiments, bearing on the effect of mechanical overload on LBT in bones adapted to a customary MU level, were reported and the results are ambiguous [41–43]. Application of impact loads to the sole of a rabbit's hindleg paw produced a definite increase in LBT, hence BMUs activation frequency in the lumbar vertebrae (i.e., vertebrae in line of the transmitted impacts) but none in the long bones of the hindleg [41]. It was postulated that in areas of increased BMU activation frequency, the latter represents a repair reaction triggered by the microdamage produced under such circumstances [44]. However, the increase in BMU activation and in microdamage production could occur independently; in BMU activation because of MU enhancing BMU activation, the macrodamage production because of the effect of the overload on the unadapted bones, the final result, occurrence or absence of stress fractures, depending on whether or not the LBT would "catch up" with the rate of microdamage production, the eventual adaptation eliminating it effectively [45].

The question then arises as to what extent *acute* disuse and *acute* overload effects do reveal how the BMU-based LBT contributes to *long-term* progressive adaptations to mechanical demands? Experiments bearing on it are difficult to devise, but nature provides us with a model, the so-called remodeling map [46] which may offer some clues.

"Remodeling" Map

Differences in BMU-based LBT in the spongiosa and the compacta and between various parts of the skeleton were noted quite early [47], but Amprino and Marotti [48] were the first to systematically study the LBT topography in the dog and to establish the "remodeling map" [46], which Kimmel and Jee [49], in so far as the spongy bone is concerned, further elaborated.

LBT was found highest in the spongiosa of the axial skeleton, whereas in the appendicular skeleton higher in metaphyses than epiphyses and in proximal metaphyses than distal ones. The highest values were recorded in the vertebral bodies, pelvis, proximal humerus, and proximal and perhaps distal femur [48, 49].

During growth, the intensity of LBT in the spongy parts, metaphyses particularly, may reflect the mechanism maintaining the trabecular pattern of bones rapidly increasing in size [9, 48]; but its persistence after the cessation of growth cannot be so explained. The greater specific surface (i.e., the bone surface to volume ratio of the spongiosa) could account for it, since any systemic factor would affect predominantly spongy bone. But spongy and compact parts of the skeleton as well show marked regional differences in LBT charac-

teristic for the dog regardless of sex [48, 49] and age [48], although the LBT rate within these patterns during growth is faster than in the adult skeleton [48].

Although a rough correlation with the red versus yellow bone marrow content could be established (bones containing red marrow showing higher LBT [50, 51]), this would not explain the differences in LBT rate in the diaphyses of various long bones—low in the mid-diaphysis of the humerus and femur, highest in the tibia, ribs, radius, and metatarsals [46].

It is tempting, therefore, to suggest that the "remodeling map" in the dog, at least in part, is determined by biomechanical factors, and that the regions of the skeleton particularly challenged mechanically show the fastest LBT; that would imply a stimulating effect of MU on BMU activation.

While it may be so, the question arises as to why the high BMU activation persists in such areas as if the transient situation were perpetuated? That could be explained by two types of adaptation imposed by the skeleton's genotype. The first would be structural, achieved mainly by bone mass adjustments, and the second would be an ongoing dynamic achieved by adjusting bone's materials properties. Thus, during phylogeny, natural selection would favor in some parts of the skeleton, mainly spongy para-articular, less mass and weight than in the diaphyses [52]. In the former, the process of creating primary and secondary spongiosa with its associated bone marrow proliferation would limit the amount of bone produced per unit volume in contrast to the diaphysis, which may grow transversally by apposition of bone on the periosteal surface. Thus, in diaphyseal compacta, *structural* adaptations to MU predominate via the adjustments of bone mass. Once adaptation is completed, the LBT activity there is low since the stimuli that even peak strains generate [53] would be in general, in structurally adapted bone, below the threshold of genetically set sensitivity of "mechano"-receptors (i.e., below MES) [39]. In the spongy parts and diaphyses of smaller weight-bearing bones where the adjustment by the increase in bone mass is limited, the high LBT would be perpetuated because strains continue to generate stimuli that exceed the threshold of "mechano"-receptors sensitivity (i.e., MES) [39]. The MCSk is maintained there instead by high quality *materials properties,* that is, reduced mean bone age and greater compliance as well as associated adjustments in the second and third order structures are the result of increased BMU activation frequency and high LBT.

If the mechanical factors such as weight bearing and muscular exertion indeed accounted for the "remodeling map" in a quadruped such as the dog, in a biped, such a map should show differences corresponding to the expected mechanical loads pattern. Unfortunately in man, such a map has not yet been completed. All that can be said is that if the effect of MU were to depress the BMU activation, such dynamic adaptations along with the adjustment in second and third order structures could not occur, with adverse consequences for MCSk. In fact, the regions of the skeleton with the high LBT activity also appear most vulnerable to interference with its operation. This may explain the occurrence of fractures often due to a minimal trauma, so-called "J" fractures [54] seen in various metabolic bone diseases in such "strategic" locations as ribs, vertebrae, upper femur and humerus, distal radius, pelvic rami, etc. [19, 54, 55].

One could claim that while reflecting the distribution and intensity of loading, the "remodeling map" would represent not the direct effects of MU on EO LBTS but rather an appropriate response to microdamage, with the same end result for MCSk [44, 45]. However, persistence of this LBT pattern or map throughout growth, when the mean bone age is low and its compliance is high, suggests that MU may affect the BMU-based LBT directly.

Concluding Inferences and Remarks

The BMU-based LBT may be viewed as an instrument that adapts bones to their MU, whereby the MCSk established during growth continues to be maintained. Apart from mediating adjustments of bone mass to mechanical demands on the periosteal and endosteal envelopes (preservation of bone mass in adults), the BMU-based LBT may contribute to the MCSk by realigning second and third order structures as well as maintenance of materials properties of bone. Each of these features may acquire a special importance on a given envelope or bone region ("remodeling map").

Although skeletons may never become perfectly adapted to their MU, one should distinguish the BMU-based LBT activity in a given region of the skeleton that is adapted to a particular level of MU, from what happens during shifts from one level to another when new adjustments of bone structure and its material properties are actually taking place.

At least in the dog, even in steady-state situations, the BMU activation frequency differs on various envelopes and regions of the skeleton so it displays a "remodeling map" which may in part reflect how the skeleton's genotype influences the

type of the prevailing adaptation. Consequently, in parts of the skeleton where structural adaptation by increasing bone mass is difficult, MU continues to maintain a high level of BMU activation which maintains MCSk because of good materials properties attributable to reduced mean bone age and greater compliance as well as to adjustments in the second and third order structures.

It would appear that both the increase of MU and its complete withdrawal may activate BMUs, possibly in each instance by different means. Thus, an upward shift of MU, in addition to enhancing BMU activation, would mitigate bone resorption by reducing recruitment and/or function of osteoclasts after activation. At the same time it would enhance bone formation by increasing recruitment and function of osteoblasts within BMUs, thereby making the balance on the periosteal envelope (where MDE < MWT) more positive and the endosteal balance (where MDE > MWT) less negative, causing overall bone balance to be less negative. Under such circumstances, increased BMU activation would help to maintain MCSk by realigning the second and third order structures, and by bone renewal it would improve the materials properties of bone tissue as well. The rapidity of any upward shift in MU and the difference between its initial and new level could determine how the BMU-mediated structural and/or materials adaptation influenced the production and accumulation of microdamage.

Thus, if MU had to inhibit BMUs activation, it would prevent all the adjustments in bone structure and its material properties. This would be against the overall design and function of the BMU-based LBT which in large part consist of maintaining the MCSk by such means.

A downward shift in MU (but short of complete withdrawal) would increase recruitment and/or function of osteoclasts within BMUs, and thereby increase the bone resorption. By also decreasing osteoblast recruitment and/or function, and thereby bone formation, a downward shift would render the bone balance on the periosteal envelope (where MDE < MWT) less positive and the endosteal balance (where MDE > MWT) more negative, to cause an overall more negative bone balance. The rapidity of the downward shift and the difference between the initial and new level of physical activity would determine the degree and rapidity of bone loss.

Sudden *complete* withdrawal of mechanical loading, on the other hand, would trigger a bone loss on a specific envelope mediated not by BMUs (MDE vs MWT) but by resorption drifts due to increased activation of osteoclast populations and a suppression of osteoblast recruitment (uncoupling).

A distinction should be made in this regard between strains sufficiently strong to affect the "mechano"-receptors of EO LBTS or MES of Frost [37] and strains below that level which, however, would be sufficient in structurally adapted bones to prevent the disuse reaction, that is, to inhibit the factors to which EO LBTS responds when MU is totally withdrawn. Thus, the strain-generated stimuli and factors affecting the EO LBTS when MU is withdrawn may be different in kind, underscoring the observation that the osteoclast populations may be activated by more than one factor or agent.

Because osteoclast populations may also be activated directly by nonbiomechanical factors (hormones, growth factors, cytokines, etc.) with varied effects on the BMUs evolution and their collective outcome, such factors may modulate the effects of MU or vice versa, as shown by Lanyon and Rubin [15, 56]. When in excess or deficient, nonbiomechanical factors may interfere with the presumed primary function of BMU-based LBT (i.e., responses to its MU) and produce various structural alterations that can cause bone fragility and predispose to fracture in strategic locations.

These inferences and conclusions, though tentative, may nevertheless offer a framework on which to integrate the wealth of data derived from clinical observations and studies as well as from research on the cellular and molecular levels that pertain to the locomotor system's physiology and pathology.

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