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The "Muscle-Bone Unit" in Children and Adolescents

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In former views hormones, calcium, vitamin D and other humoral and nonmechanical agents dominated control of postnatal bone strength (and "mass") in children and adolescents. However later evidence that led to the Utah paradigm of skeletal physiology revealed that this control depends strongly on the largest mechanical loads on bones. Trauma excepted, muscles cause the largest loads and the largest bone strains, and these strains help to control the biological mechanisms that determine whole-bone strength. That makes the strength of children's load-bearing bones depend strongly on growing muscle strength and how bones respond to it. Most hormones and other nonmechanical agents that affect bone strength can help or hinder that "bone strength-muscle strength" relationship but cannot replace it. In addition some agents long thought to exert bone effects by acting directly on bone cells, affect muscle strength too. In that way they could affect bone strength indirectly. Such agents include growth hormone, adrenalcorticosteroid analogs, androgens, calcium, vitamin D and its metabolites, etc. Thus bone and muscle do form a kind of operational unit. It is part of the Utah paradigm that supplements earlier views with later evidence and concepts. The paradigm explains how the "bone strength-muscle strength" relationship works. This article provides a mini overview of that physiology.

The Utah Paradigm

This now stands on compelling evidence. In part it includes testing in pioneering live-animal experiments in Prof. Jee's laboratory at the University of Utah. Still, before 1998 one of its tenets caused controversy. To wit: *Neuromuscular anatomy and function strongly influence, and could even dominate, control of the biologic mechanisms that determine the postnatal strength of load-bearing bones*. But by 2000 AD, bone-muscle-strength comparisons in over 1,800 healthy humans from 2 to over 80 years of age strongly support this idea. *How could muscle do that to bone?* Some of the Utah paradigm's answers follow.

Control of Modeling and Remodeling by Mechanical Factors

Mechanical loads on bones deform or strain them, and larger loads cause bigger strains. Where dynamic bone strains exceed a *modeling threshold* range, modeling increases bone strength. That lowers later strains towards the bottom of this threshold mechanically-controlled modeling stops. Accordingly modeling normally makes bones strong enough to keep "typical peak strains" from exceeding its threshold. When dynamic strains stay below a lower *remodeling threshold* range, disuse-mode remodeling removes bone but only next to marrow. That reduces the amount of trabecular bone, it expands the marrow cavity and it thins the cortex. These changes cause a "disuse-pattern osteopenia".

Control of Modeling and Remodeling by Endocrine and Other Nonmechanical Factors

In contrast to former views, in children and adolescents most items can help or hinder but cannot replace the responses of modeling and remodeling to bone strains. As examples, hormones, calcium and vitamin D might determine from 3% to as much as 10% of our postnatal bone strength, but natural experiments show mechanical usage effects determine over 40% of it. In proof, lower but not upper extremity bones can lose over 40% of their original strength some years after a paraplegia. The lower limb bones of patients paralyzed by a myelomeningocele show even larger such deficits. Such things question the idea that genetic factors in bone's effector cells could predetermine over 70% of our postnatal bone strength.

The Role of Momentary Muscle Strength

Muscles work against such bad lever arms that it takes well over two kilograms of muscle force on bones to

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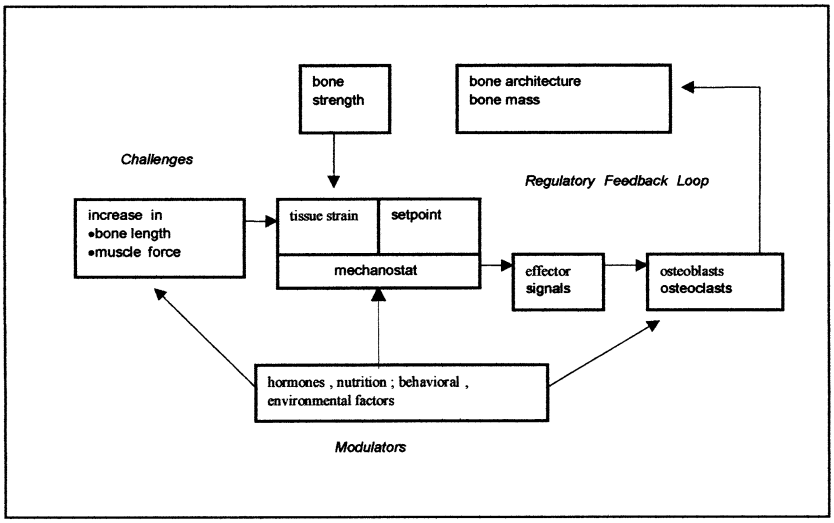

Fig. 1. A functional model of bone development based on mechanostat theory. The central piece of bone regulation is the feedback loop between bone deformation (tissue strain) and bone strength. During growth this homeostatic system is continually forced to adapt to external challenges. Factors shown below modulate various aspects of the central regulatory system.

move each kilogram of body weight around on earth. The largest voluntary loads on load-bearing bones come from muscle forces, *not* body weight. Thus momentary muscle strength strongly influences postnatal bone strength. Momentary muscle strength also usually increases during growth, plateaus in young adults and then declines. Less than half of our young adult muscle strength remains at 80 years of age. Some factors long thought of affect bone strength by acting directly on osteoblasts and/or osteoclasts, affect muscle too. Such factors include growth hormone, androgens, adrenalcortical steroid analogs, calcium, vitamin D and exercise. Yet bone and muscle do form a kind of functional "bone-muscle unit" in which changes in momentary muscle strength should and usually do affect bone strength predictably and correspondingly.

The Mechanostat Hypothesis

The combination of factors that makes healthy load-bearing bones satisfy in all amphibians, birds, mammals and reptiles of any size, age and sex was named the mechanostat. It would combine the modeling and remodeling mechanisms, their thresholds, the marrow mediator mechanism, the signaling mechanisms that connect them, and perhaps other things. The resulting negative feedback system would determine whether, when and where bones needed more strength, or when bone was not needed for mechanical reasons. Various nonmechanical factors, including hormones and other humoral agents, might modulate ("help or hinder") the mechanostat's effects on bone strength. The mechanostat would be like the *combination* of a car's steering, brakes and accelerator. Osteoblasts and osteoclasts would be like the car's wheels, and mechanical usage would be like its driver (Figure 1).

Two Meanings of "Vigorous" Exercise

Low-force activities done to exhaustion, such as long distance running, swimming and bicycling, increase muscle endurance but not bone strength. *Maximal-force* activities, such as weight lifting, or sports that involve violent accelerations of the body, put larger loads on bones than low-force exercise. As a result weight lifters and soccer players have greater bone strength than devotees of low-force exercises.

While excellence in many sports requires great power and good neuromuscular coordination, bone strength seems to adapt more to peak *momentary* (isometric) muscle forces. This suggests corresponding kinds of exercise during growth could help to achieve greater bone strength and minimize fractures later on in adult life.

Implications of the Above Physiology

Regarding the applications of the muscle-bone relationship in clinical practice, we propose the two-step diagnostic algorithm. Required are a measure of muscle force or size and a measure of BMC at a corresponding location. The results can be combined into four diagnostic groups. In the first situation, muscle force or size is adequate for height. If simultaneously BMC is normally adapted to the muscle system, the result is interpreted as "normal". If BMC is lower than expected for muscle force or size, a 'primary bone defect' is diagnosed. In the second situation, muscle force or size is too low for height. Even if BMC is adequately adapted to the decreased mechanical challenge, this means that bone mass and presumably strength are still too low for body height. Therefore, a "secondary bone defect" is diagnosed. If muscle force or size is abnormally low and BMC is even lower than expected from a normal muscle-bone relationship, a "mixed bone defect" (primary and secondary)

is present. This diagnostic procedure resembles a classification of disorders with low bone mass which was proposed by Frost. He distinguishes "true osteoporosis", "physiologic osteopenia", and "combination states".

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