Focus on voluntary run training but not estradiol deficiency alters the tibial bone-soleus muscle functional relationship in mice: fracture and mechanostat

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IN THIS ISSUE OF the American Journal of Physiology-Regulatory, Integrative, and Comparative Physiology, Warren et al. (14) presented the finding that voluntary wheel running in mice increased the muscle-to-bone strength ratio independent of estrogen status. Although there were no detrimental effects of the increased muscle force on bone caused by the muscle-to-bone strength imbalance, it was concluded that such an imbalance over time could lead to stress fracture. This editorial focus will discuss these results in the context of two opposing theories of stress fracture etiology. The first theory is that increased muscle mass places increased strain on bone, increasing susceptibility to stress fracture development. The second theory is that increased muscle mass is protective because it stabilizes the bone against bending forces.

In addition, Warren et al. (14) found that the beneficial effects of exercise on bone were similar in ovariectomized and sham mice, despite the fact that ovariectomized mice voluntarily ran five times less distance on a daily basis than sham mice. This has implications for the “mechanostat” theory of bone formation, which refers to the degree to which strains from loading are detected by bone and translated into the process of increased bone formation (5). The findings of Warren et al. would imply that estrogen deficiency makes bone more sensitive to the positive effects of exercise.

ETIOLOGY OF STRESS FRACTURE

The main purpose of the study by Warren et al. (14) was to determine the independent and combined effects of two major risk factors for stress fractures, estrogen deficiency and run training, on the bone-muscle functional relationship. Young female adult mice were used in the study.

There are contrasting theories on the relationship of bone to muscle strength and susceptibility to stress fracture. The first theory predicts that exercise training increases muscle strength more than bone strength, with the increased force of muscle contraction through its attachment to bone causing bone injury. The second theory predicts that the increase in muscle strength is protective; that is, muscle acts as a shock absorber to lessen cortical bending and strain during running. With the animal model, Warren et al. (14) found that short-term training induced an increase in the strength of muscle relative to bone; however, this did not increase the bone’s susceptibility to fracture in direct bending tests of ultimate strength. They concluded that the longer the muscle-to-bone functional capacity mismatch continued to exist, the greater would be the chance for occurrence of a stress fracture.

There is some evidence from studies of humans that support this theory. Beck et al. (2) measured muscle cross-sectional area at the midtibial and predicted bone strength from structural analyses of the femur and tibia using dual-energy X-ray absorptiometry in 1,288 male and female Marine recruits before a 12-wk training program. Comparisons were made between those who suffered stress fractures (n = 75) and controls who did not suffer stress fractures (n = 1,213) during the training program. Midthigh muscle cross-sectional area, a surrogate of muscle strength, was significantly lower by ~4% in those with stress fractures vs. controls, lending some support to the theory that muscle weakness may lessen the ability to absorb the cortical bending of bone during running. Predicted bone strength at the tibia and femur, however, was ~7% lower in those with stress fractures, indicating that they would have had a greater muscle-bone strength before training than controls, supporting the theory that muscle may impart forces through its attachment to relatively weaker bone causing damage. It should be noted that all muscle and bone measurements were made before the 12-wk training program. It would be of interest to evaluate changes in muscle and bone during such a training program to see whether the muscle-bone strength imbalance increases, as would be predicted from the study by Warren et al. (14).

One final finding from studies of humans supporting the theory that excessive muscle pull on bone may induce stress fracture comes from a study involving stress fracture in the upper limbs of athletes involved in swimming, throwing, or tennis (3). These sports would involve much less impact loading than shown in running, and the predominant forces on the bone would be from muscle contraction. On the basis of the findings of Warren et al. (14) and Beck et al. (2), it would be of interest to evaluate the effects of strength training before exposure to a prolonged run-training program to determine whether increased muscle-bone strength is protective against or increases stress fracture.

Warren et al. (14) did not discuss one finding from their study in support of the alternative theory that muscle strength may have a protective effect by preventing cortical bending and strain during running; that eccentric strength of the soleus was increased with their running program. One study in humans indicated that eccentric strength of the plantar flexors is important for opposing the large forward bending moment of the tibia caused by ground reaction forces during running (13). A limitation of the study by Warren et al. (14) is its short duration. As mentioned by Warren et al., longer studies are required to determine whether increased muscle strength to bone strength during training will damage or protect bone.
ESTROGEN AND THE MECHANOSTAT

An interesting, unintended finding of Warren et al. (14) was that voluntary wheel running had an equally positive effect on bone properties (specifically an increase in elastic modulus, which led to an increase in stiffness of the tibia) in ovariectomized and sham mice despite the fact that the voluntary daily running distance by ovariectomized mice was five times less than that of sham mice (i.e., 1.45 vs. 7.35 km/day). This implies that estrogen deficiency increases the sensitivity of bone for translating mechanical strain into beneficial adaptations in the bone.

The mechanostat theory states that exercise increases bone formation when the mechanical strain exceeds a threshold called the minimal effective strain (4). There are two opposing theories on the effects of estrogen on the setting of this minimal effective strain. One theory is that estrogen lowers the minimal effective strain, causing estrogen to enhance the positive effects of exercise on bone (9, 12). The opposing theory is that estrogen actually opposes the beneficial effects of exercise, effectively raising the minimal effective strain (6, 11). The positive or negative effects of estrogen on exercise-induced bone adaptation may depend on the estrogen receptor subtype and the bone surface (i.e., endosteal or periosteal surface) studied. Saxon and Turner (11) outlined a theory in which estrogen receptor-β activation on the periosteal bone surface causes attenuation of exercise-induced bone formation, whereas estrogen receptor-α activation causes an enhancement of exercise-induced bone formation on the endocortical and trabecular bone surfaces. The prevention of periosteal bone formation would prevent an expansion of bone size, which is necessary for enhancement of bone strength, whereas bone formation on the endocortical surface would have a minimal effect on increasing bone size and strength. This theory is supported by two findings. First, in humans, the ability of exercise to induce an increased periosteal expansion and therefore bone strength is greater before puberty in females, when estrogen is low, compared with after puberty, when estrogen levels are high (1, 7). The estrogen surge at puberty allows more bone to be added to the endocortical surface in response to exercise, but this has a minimal effect on predicted bone strength (1). Second, the skeletal responsiveness to mechanical loading in mice is enhanced with a null mutation in estrogen receptor-β. Specifically, periosteal bone formation in response to mechanical loading of the ulna was enhanced in female mice lacking estrogen receptor-β (10). In direct contrast, Lee et al. (8) found that bone formation on the periosteal surface in response to mechanical loading of female mice ulnae was prevented if mice were deficient in either estrogen receptor-β or estrogen receptor-α. The findings of Warren et al. (14) that sham mice experienced a beneficial response to exercise (i.e., increased elastic modulus and bone stiffness) similar to ovariectomized mice despite running five times more distance on a daily basis support the theory that estrogen raises the minimal effective strain for a beneficial effect of exercise on bone. It should be pointed out that the beneficial effects of exercise in the study of Warren et al. were relatively small (i.e., a small increase in bone stiffness and no change in ultimate load); therefore, definite conclusions regarding estrogen and its effect on the mechanostat cannot be made.

Although benefits were small, the finding that the effects of exercise on bone were induced with a much smaller training volume in ovariectomized mice is encouraging if applied to postmenopausal women. This would imply that postmenopausal women may be able to realize benefits on bone with a much lower training volume than their premenopausal counterparts. Measurement of changes in bone geometric properties in response to exercise training programs in pre- vs. postmenopausal women is needed to confirm this hypothesis.

REFERENCES