Published in final edited form as:

Bone. 2010 February ; 46(2): 272. doi:10.1016/j.bone.2009.12.024.

Muscle loss and bone loss: master and slave?

Alexander G. Robling, Ph.D.

Department of Anatomy and Cell Biology, Indiana University School of Medicine, 635 Barnhill Dr., MS 5045, Indianapolis, IN 46202, Tel: (317) 274-2315, Fax: (317) 278-2040

Alexander G. Robling: arobling@anatomy.iupui.edu

Among the ever-growing list of benefits associated with physical activity, bone and muscle health remain near the top. Exercise improves muscle strength, and simultaneously enhances bone architecture and fracture resistance. The strong association between these two parameters has been explored in greater detail in recent years, to begin to understand the extent to which muscle might play a governing role in bone adaptation. This role has practical implications, for if muscle does govern bone, then physical activity exercises should be targeted to primarily maximize muscle strength, and the bone will follow. Despite early claims of a cause-effect relation, based on anecdotal evidence, individual case studies, or orthopaedic experience, experimental data directly addressing this issue have been scarce.[1] Perhaps the lack of progress in this arena can be linked to a paucity of suitable animal models. With the exception of tail suspension studies, which have their own limitations (e.g., fluid shift), it has been difficult to experimentally (and non-surgically) reduce and subsequently restore muscle function without directly affecting the adjacent bone.

More recently, development of the Botox reversible muscle-paralysis model of disuse[2] has circumvented many of these concerns, and has ushered in the potential to more directly address some cause-effect questions regarding the regulatory role of muscle forces on bone properties. Moreover, the recent generation of high resolution *in vivo* μ CT technology has permitted the opportunity to track small changes in bone and muscle size noninvasively over long periods of time, i.e., through muscle paralysis and subsequent recovery. In this issue of *Bone*, two independent groups report the results of several elegant Botox-induced muscle paralysis experiments in mice, which monitor longitudinal changes noninvasively in muscle size and bone mass over a 12–16 wk post-paralysis period.[3,4] These two studies highlight some interesting, novel, and remarkably consistent findings that address the role of muscle size/function on bone mass and architecture.

LOSS OF MUSCLE STRENGTH, MUSCLE SIZE, AND BONE PROPERTIES

Two issues are central to demonstrating a cause-effect relation between muscle strength and bone mass: (1) loss of muscle function precedes loss of bone mass and (2) return of muscle function precedes the return of bone mass.[1] Both Manske et al.[3] and Poliachik et al.[4] report a peak reduction in calf muscle volume at 2–4 wks post-paralysis. Similarly, proximal tibia trabecular bone volume fraction and tibial cortical area were maximally reduced at 2–4 wks post-paralysis. The remarkably similar muscle loss and bone loss trajectories leave no indication of a lag phase between muscle loss and bone loss. However, as the authors point

Correspondence to: Alexander G. Robling, arobling@anatomy.iupui.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

out, that does not preclude a functional lag. Impaired muscle function can be detected within hours of Botox injection. Pickett et al.[5] injected various concentrations of Botox into the calf muscles of rats and measured muscle force generated by 100V stimulation of the sciatic nerve (Figure 1). They found a Botox dose response in force output, reaching 75% reduction in force output 24 hrs (their earliest time point) after a 3 U/kg Botox injection. Manske et al. and Poliachik et al. used higher doses (10 and 20 U/kg, respectively), so it is reasonable to assume that muscle function was at its lowest level in the 12–24 hrs post-injection time range in these studies. In support of this assertion, Poliachik et al. confirmed an early loss of muscle function indicated by the loss of plantarflexion after 24 hrs. Thus, the loss of muscle function precedes cortical and trabecular bone loss by several weeks, but surprisingly, an equally large lag time exists between the loss of muscle function and size.

RESTORATION OF MUSCLE STRENGTH, MUSCLE SIZE, AND BONE PROPERTIES

While it is reasonable to conclude that the Manske et al. and Poliachik et al. studies support a cause–effect relation between the loss of muscle strength (but not size) and the loss of bone mass, both studies are consistent in highlighting the complexity of the return of muscle function on bone properties. Both studies demonstrate a partial but incomplete recovery of original muscle volume by the end of the study (after 12 or 16 wks post-paralysis). Likewise, both studies demonstrate a marginal, if any, recovery of proximal tibia trabecular bone volume fraction. However, both studies convincingly demonstrate a full recovery of tibial cortical bone volume prior to the conclusion of the study. This result is somewhat ironic – in setting out to elucidate whether muscle recovery precedes bone recovery, a clear result indicating that (cortical) bone recovery precedes muscle recovery emerges. These observations prompt several questions: (1) Is cortical bone recovery independent of muscle function/mass? (2) Why does cortical bone recover and trabecular bone fail to recover?

Regarding the former question, a survey of the literature indicates that much like the lag time between Botox-induced loss of function and loss of muscle mass, a potentially greater lag exists between restoration of muscle function (following the “wearing off” of the Botox effects) and muscle mass (Figure 2). For example, Ma et al.[6] found that muscle function began to approach pre-paralysis levels after approximately 10 wks post-paralysis, whereas muscle mass took roughly 26 wks to approach normal levels, with a full year required to statistically reach control values. The first 16 weeks-worth of muscle mass data mirror those reported for muscle size in Manske et al. and Poliachik et al. almost exactly, and suggest that muscle function might have been restored in their studies well before the end of the experiment. If so, the recovery of cortical bone mass could be accounted for by muscle forces, but that would not leave much room for a lag phase between muscle force recovery and bone mass recovery. Such an explanation would not, however, account for the lack of recovery in trabecular bone.

But the trabecular bone response might not be so difficult to reconcile if all of the data are considered. A closer look at the μ CT results by the authors show that disuse decimates trabecular bone surface area by removing whole trabeculae (Tb.N was reduced in both studies and did not recover), which any subsequent osteogenic recovery would require in order to restore baseline bone mass. The opposite is true on the endocortical surface, which actually increases its available surface area (for subsequent bone formation during recovery) as a result of disuse-mediated resorption. The loss of whole trabeculae appears to be an irreversible consequence of Botox-induced disuse, but both studies show clearly that bone formation activity *on the surviving trabeculae* does recover completely, as revealed by changes in trabecular thickness (Tb.Th). Those data mirror the cortical volume data, and suggest that on the cellular level, both trabecular and cortical bone show similar trends in loss and recovery following muscle paralysis. The fact that new lamellar bone formation can not occur *de novo*

(i.e., without a preexisting surface on which to begin laying down new bone) can reconcile the apparent discrepancy between cortical and trabecular bone mass recovery following restoration of muscle function. As with the recovery of cortical bone volume, the question that remains is whether the return of muscle function preceded the return of trabecular thickness. If so, the data of Manske et al. and Poliachik et al. are completely consistent with a cause–effect relation between muscle strength and bone mass.

A MUSCLE-DRIVEN MECHANOSTAT?

The literature is clear that muscle forces per se are capable of providing a sufficient stimulus to drive bone adaptation. Whether muscle forces provide the main stimulus is still under question,[7] but the data presented by the Manske et al. and Poliachik et al. articles in this issue of *Bone* provide novel insight into the muscle- and bone-wasting trajectories accompanying disuse, and the nature and timing of their return following a gradual restoration of muscle function. These studies, in conjunction with other studies that have monitored muscle function after Botox, are consistent with a muscle-driven mechanism for bone adaptation. Future paralysis–recovery experiments that include noninvasive serial measurements of muscle function,[5] in addition to longitudinal monitoring of muscle and bone mass/architecture, could shed even more light on the role of muscle strength in determining bone mass. Muscle therapy, via either physical activity or pharmacological intervention, remains a potentially high-yield strategy for improving bone mass and preventing fractures.

References

1. Burr DB. Muscle strength, bone mass, and age-related bone loss. *J Bone Miner Res* 1997;12:1547–51. [PubMed: 9333114]
2. Warner SE, Sanford DA, Becker BA, Bain SD, Srinivasan S, Gross TS. Botox induced muscle paralysis rapidly degrades bone. *Bone* 2006;38:257–64. [PubMed: 16185943]
3. Manske SL, Boyd SK, Zernicke RF. Muscle and bone follow similar temporal patterns of recovery from muscle-induced disuse due to botulinum toxin injection. *Bone*. 2009
4. Poliachik SL, Bain SD, Threet D, Huber P, Gross TS. Transient muscle paralysis disrupts bone homeostasis by rapid degradation of bone morphology. *Bone*. 2009
5. Pickett A, O’Keeffe R, Judge A, Dodd S. The in vivo rat muscle force model is a reliable and clinically relevant test of consistency among botulinum toxin preparations. *Toxicon* 2008;52:455–64. [PubMed: 18639570]
6. Ma J, Elsaidi GA, Smith TL, Walker FO, Tan KH, Martin E, Koman LA, Smith BP. Time course of recovery of juvenile skeletal muscle after botulinum toxin A injection: an animal model study. *Am J Phys Med Rehabil* 2004;83:774–80. quiz 781–3. [PubMed: 15385786]
7. Judex S, Carlson KJ. Is bone’s response to mechanical signals dominated by gravitational loading? *Med Sci Sports Exerc* 2009;41:2037–43. [PubMed: 19812513]
8. Stone AV, Ma J, Whitlock PW, Koman LA, Smith TL, Smith BP, Callahan MF. Effects of Botox and Neuronox on muscle force generation in mice. *J Orthop Res* 2007;25:1658–64. [PubMed: 17600825]

Figure 1.

Injection of botulinum toxin A into the calf muscles of rats induces severe and lasting muscle paralysis. While earlier studies found that doses higher than 3 U/kg yield no dose response with muscle force generation, injecting under 3 U/kg does yield a dose-response. Moreover, doses in the 0.1 U/kg range induce mild paralysis that is completely restored after 6 wks (indicated by termination of the square-points curve at 6 wks). Stone et al.[8] reported complete recovery after only 4 wks using a 3 U/kg dose. Lower doses could be used in bone studies to more quickly return muscle function, but it is unclear whether the initial decrease in muscle function is large enough to induce measureable changes in bone mass. Redrawn after reference [5].

Figure 2.

Injection of botulinum toxin A into the calf muscles of rats induces rapid loss of muscle function and mass, but the recovery of muscle mass, relative to function, is severely delayed. Whereas muscle function took ~10 wks to return to baseline values, muscle mass required 1 year to return to baseline values. These trajectories highlight the large “lag” phase between muscle strength (e.g., force generation) recovery and muscle mass (area, volume, weight) recovery, and temper our interpretation of muscle size on function. Drawn from data presented in Ma et al.[6]