

What is new in neuro-musculoskeletal interactions?

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Muscles are weaker but bones are bigger (or maybe not) in renal failure

Patients on hemodialysis have a markedly increased incidence of fracture, but in most cases bone mineral density is within normal limits. So they must have bad bone quality, right? There are probably few renal bone disease experts who would argue with this statement, even though it is possible that fewer still might agree on what they actually mean by "bone quality". Jamal et al. circumnavigate the nebulous field of bone quality by focusing instead on the importance of the neuromuscular system in such patients. The authors hypothesized that "neuromuscular function would be significantly correlated with fracture in hemodialysis patients"¹. And this is indeed what they found in a study of 52 patients who had been on hemodialysis for more than a year. There was no association between fractures and bone mineral density at the hip or spine. In contrast, better muscle performance (such as timed up and go test and distance walked in 6 minutes) was associated with a reduced risk of fracture. That leads to the conclusion that it may be useful to do more muscle-oriented testing in hemodialysis patients. So is it time to add "muscle quality" to our repertoire of foggy buzzwords?

It may be more rewarding to turn to high quality research instead, such as that provided by the strong group from Tampere, Finland. Jokihaara and colleagues examined the effects of mild renal failure on whole-bone structure in a rat model². Using peripheral quantitative computed tomography to examine the femoral neck and midshaft, they found that already a moderately impaired renal function led to a significant loss of bone mineral. However, this loss of bone mass was associated with a simultaneous increase in the total cross-sectional area of the femoral neck. The increase in

bone size apparently compensated for the loss of bone mass and the mechanical integrity of the bones was maintained. The authors see in this the workings of the mechanostat, which maintained bone structural strength constant even in the face of adversity.

In a second study, the same authors used the same approach, but let the renal failure progress a little longer³. This resulted in a model of more severe renal failure and apparently also a more severe bone disease. In any case, biomechanical testing now showed a decreased breaking load in the uremic rats. What is a bit surprising is that there was no sign of a compensatory increase in femoral neck size in that second study. We learned from the previous study that femoral necks expanded in moderate renal failure. So the normal bone size following longer progression of renal failure suggests that femoral necks shrink as the rats go from moderate to severe uremia, correct? The authors elegantly avoid this thorny question by simply not cross-referencing the two papers, thereby stimulating readers to do the thinking themselves.

Botox: Beyond beauty

To the general public, botulinum toxin (Botox[®]) is best known for decreasing frown lines. New research using this drug, however, is raising eyebrows, at least among bone specialists. Warner et al. examined the effect of intramuscular botulinum toxin injections on bone⁴. The idea behind this study was that botulinum toxin induces flaccid paralysis of injected muscles by blocking neuromuscular transmission. This unloads those bones to which the injected muscles are attached. In their study, Warner et al. injected botulinum toxin into the gastrocnemius and calf muscles of mice. Three weeks later, they observed what they labeled "a profound degradation of muscle and bone". The mass of the injected muscles was decreased by about half, as was the amount of trabecular bone in the distal femur and proximal tibia. This observation, so the authors conclude, confirms "the decisive role of muscle contraction in maintaining bone mass".

An important piece of information is missing in that study, however: to what extent did botulinum toxin decrease the force of the injected muscles? Fortunately, Longino et al.

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provide some data on this topic, albeit in rabbits⁵. These investigators injected botulinum toxin once into the quadriceps of adult New Zealand rabbits. One month later, isometric knee extensor torque on maximal electrical stimulation was 68% weaker on the injected side, as compared to the contralateral leg. When the rabbits jumped on a force plate, the peak push off force was 37% lower in the injected versus the contralateral hind limbs. Interestingly, the authors of this study are not 'bone people' but have a focus on arthritis and hope to use this model as a tool to investigate the role of muscle weakness in joint degeneration. Thus, botulinum toxin may have only a short-lived effect on your frown lines, but these botulinum-based models could make a long-lasting impact on musculoskeletal research.

Shocking: Dense vertebral bodies squeezed hard by eccentric flexors!

Lumbar spine bone mineral density readings have the annoying tendency to decrease after menopause. Armies of researchers from academia and industry are trying to solve this problem, which by itself suggests that their efforts have not been overwhelmingly successful until now. Undaunted, Iki et al. have contributed their own piece to the billion-dollar puzzle⁶. They followed 109 healthy postmenopausal women for four years and compared the rate of change in lumbar spine bone density to baseline trunk muscle tests. They found a positive correlation between the change in bone mineral density and eccentric trunk flexor and extensor torques. The lower tertile group for the extensor torque showed a ten-fold greater risk for rapid bone loss compared with the upper tertile group. Iki and colleagues therefore think that osteoporosis prevention "should include an exercise program designed to increase the strength of the trunk muscles".

All too often, however, all preventive measures come to naught and vertebral compression fractures do occur. It is well known that the risk of further vertebral fracture increases greatly after an initial vertebral fracture, regardless of bone mineral density. Why is that? Faced with such tricky questions, it is tempting to mumble something about "bone quality" and leave it at that. Briggs and colleagues were more ambitious⁷. They reasoned that a vertebral fracture increases the mechanical loads on the other vertebrae. An anterior wedge fracture, for example, shifts the center of mass of the trunk forward, leading to higher flexion moments. To examine this idea, they took pictures and X-rays of elderly women with low bone density and estimated "model-derived segmental vertebral loading" from T2 to L5. As compared to fracture-free study participants, women with vertebral fractures had significantly greater compression and shear forces, as well as greater flexion moments acting on the vertebrae above and below the fractures. These increased forces, the authors propose, may be responsible for the increased risk of subsequent vertebral fractures.

Vibrations: An earth-shaking treatment option?

Vibrations, once just an occupational hazard, are now being marketed as 'a highly non-invasive' 'osteoporosis treatment without drugs'. Executives in the pharmaceutical industry are not trembling with fear, for now. At present, most of the shaking seems to come in small amplitudes and is done by mice. For example, those described by Xie et al.⁸. Young (eight weeks old) female mice underwent a daily program consisting of 15 minutes of small magnitude, high-frequency whole-body vibration. Three weeks later, these mice had fewer osteoclasts in the proximal tibial metaphysis and epiphysis, but higher bone formation rates on the endocortical surface of the metaphysis. And, yes, thanks for asking, bone quality was good indeed. An amusing aspect of this report is that the final conclusion does not deal with the results of their mouse study at all, but rather is a mini-advertisement for the authors' device (stay tuned, we will be back right after this...): "If whole-body vibrations prove to be efficacious in the growing human skeleton, they may be able to provide the basis for a non-pharmacological and safe means to increase peak bone mass and, ultimately, reduce the incidence of osteoporosis or stress fractures later in life". Quick, where can I get shares of the manufacturing company?

Here we are again, back to discussing science. In a second study on young mice, Murfee and colleagues looked at the effects of small amplitude high-frequency vibrations on the vasculature of the soleus muscle⁹. Six weeks of 15 minutes daily vibration exposure caused a decrease in the number of capillaries, arterioles and venules, at least in the end region of the soleus muscle. Considering that we generally like our muscles well perfused, is this outcome good or bad? This is not clear, apparently. "The functional outcome of these adaptations remains unclear" the report concludes.

Castillo et al. used somewhat older mice (16 weeks) and studied the effect of vibration on cortical bone in the ulna¹⁰. A variety of different vibration regimes were tested, but compared to the studies mentioned earlier, the mice received homeopathic doses of vibration. The maximum exposure was just 30 seconds per day, 3 days a week, for 4 weeks. The dry conclusion from a lot of experimenting in a lot of mice is: "Vibration alone did not result in any new bone formation." However, this is certainly not the end of the story, far from it: "More long-term studies are needed to determine whether vibration at different magnitudes and frequencies than those tested in the current study, alone or superimposed onto an osteogenic waveform, can lead to or enhance cortical bone formation". As highlighted by this conclusion, vibrations come in many shapes and sizes and they can be applied in an almost limitless number of ways. Vibration studies are here to stay.

Death of the tensile trabecula?

Some concepts are intuitively so appealing that they do not seem to require testing. The very best are handed down from one generation of medical professionals to the next, like the

tools of medieval workmen. Take for example the famous analogy between the proximal femur and a crane. Over the past 150 years, probably thousands of professors have taught millions of students that the proximal femur is a beautiful example of how mechanical forces determine bone shape. Look at those structures in the lateral part of the proximal femur. These are the tensile trabeculae. And here in the medial part of the bone, you have the compressive trabeculae. Very convincing indeed, but is it true? Rudman et al. make the outrageous statement that the distribution of stress in the proximal human femur has actually never been adequately studied¹¹. They point out that previous thinking on the topic neglected the forces created by muscles and ligaments. These authors therefore developed a 2-D finite element model of the femur in which body weight, a representation of the pelvis, ligamentous forces and the hip abductor muscles were included. Including ligamentous and muscular forces into the model had the effect of generating compressive stresses across most of the proximal femur. In this model, the famous arch of 'tensile trabeculae' actually represents ordinary compression trabeculae that transmit the compressive loads from the femoral neck to the femoral shaft. Rumors of the death of the tensile trabeculae concept are nevertheless greatly exaggerated. After a century-long career through medical textbooks, they are well entrenched. Rudman et al. will face an uphill battle to get their model universally accepted.

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