

What is new in neuro-musculoskeletal interactions?

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On soups, hips and humeri (Frank Rauch)

Strong muscles prevent bone loss, fractures and death

How to study musculoskeletal interactions in clinical studies? A popular method is what might be called the 'multiple regression soup' approach. Mix a number of cross-sectional bone and muscle data, add a generous amount of confounders and stir for a while, until P values below 0.05 pop up. Such studies tend to generate conclusions like: 'Although pinch strength is a strong determinant of femoral neck bone density, trunk fat mass is a better predictor after correcting for the calcium intake of second degree cousins.' More enlightenment can be expected from longitudinal studies, such as those performed by Iki et al.¹. They followed 119 healthy postmenopausal women for four years and compared trunk muscle torque with changes in lumbar spine areal bone mineral density (BMD). Their story has a curious twist, however, because the muscle data are presented as confounders of the relationship between BMD and vitamin D receptor genotype. Nevertheless, the end result is that trunk muscle torque is related to changes in areal BMD regardless of age, body size and vitamin D receptor genotype.

Sinaki et al. are already a step ahead². They also studied healthy postmenopausal women, but their outcome measure was the real thing – fractures. Half of their study participants served as controls, the others performed resistive back-strengthening exercises for the first two years of this 10-year follow-up study. Although two years of exercise did not have any immediate effect on lumbar spine areal BMD, the exercise group had a higher BMD result after 10 years. More interest-

ingly, the incidence of vertebral compression fractures was 2.7 times higher in controls than in the exercise group. An important side aspect of this report is that the beneficial effect of exercise would have gone unnoticed if the study had been limited to the usual two or three years of follow-up. This example shows that good intervention studies not only require good compliance of the study participants, but also researchers with a great deal of tenacity – and long-term grants.

Whereas JMNI readers may have suspected the results of the BMD and fracture studies, it might still come as a surprise that strong muscles prevent the ultimate serious adverse event, death. Yet, that is what Rantanen et al. found³. They investigated a group of elderly people who had participated in knee extension strength tests and who subsequently suffered at least one bone fracture. The incidence of death following the fracture was more than four times higher in the weakest one-third of subjects than in study participants who were in the highest muscle strength tertile. The authors suggest that strengthening exercises might reduce mortality. It remains to be seen whether there is a threshold of muscle strength above which death is abolished altogether.

Hip fractures: Should we treat with electricity or hormones?

Once a hip fracture occurs, it is critical to get back on one's feet as quickly as possible. Muscle weakness is a major impediment to reach this goal. Two small pilot studies have investigated different approaches to prevent the loss or to speed up the recovery of muscle strength after hip fracture^{4,5}.

Lamb et al. used neuromuscular stimulation of the quadriceps muscle with the aim to improve muscle power after surgical fixation of a hip fracture (thereby performing the only truly neuro-musculoskeletal study of this review)⁴. Neuromuscular stimulation was applied for three hours per day for six weeks, starting one week after surgery. There also was a control group who received placebo stimulation. Neuromuscular stimulation had no detectable effect on the post-surgical increase in muscle power. Yet, the patients who received stimulation had a greater recovery of their walking speed – in the period after the stimulation phase was over. Thus, the results of this study were not really straightfor-

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ward, but the authors nevertheless were optimistic about the value of their approach.

Boonen et al. used recombinant human insulin-like growth factor I (IGF-I) complexed with IGF binding protein 3 to improve muscle and bone strength after hip fracture. The drug was administered subcutaneously between day 3 and day 59 after the fracture, using an ambulatory infusion pump. The treatment did not prevent the initial post-fracture drop in bone density (of the contralateral hip). However, patients receiving the highest dose of the hormonal complex increased their maximal isometric grip force and regained their bone density within 6 months. In contrast, patients on placebo tended to lose grip force and failed to regain lost bone. The authors cautiously point out that larger studies are needed to judge the therapeutic potential of their hormonal complex.

Tennis: Same thing around the globe

Have you ever wondered why you hear so little about Finnish tennis players in the sports news? The reason is simple. Finnish tennis players do not have time to participate in serious competitions, because they are constantly undergoing tests by the Bone Research Group in Tampere. They may not become celebrities in that way, but at least they have contributed to a considerable number of publications over the past 10 years⁶⁻¹³. In the latest of these, the authors use peripheral quantitative computed tomography to show that bone mineral content of the humerus is larger in the playing arm than on the contralateral side¹³. The difference was mainly due to a larger cross-sectional bone size – not a surprise to readers who are familiar with the mother of all tennis bone papers, the classic 1977 study by Jones et al.¹⁴. The side-to-side differences were larger in subjects who started to play before menarche than in those who started later, confirming earlier data from the same group¹⁰. So, is there anything new at all in this study? Well, it is probably the observation that side-to-side bone size differences were less at the distal radius than at the humerus midshaft, reflecting the fundamental differences in the development of metaphyseal and diaphyseal bone¹⁵.

On the other side of the globe, Bass et al. evaluated humeri of young female Australian tennis players¹⁶. They used a more complicated approach than in the above study to measure the same things, combining magnetic resonance imaging (to measure geometry) and dual energy X-ray absorptiometry (to measure bone mineral content). The results were almost superimposable to those from the Finnish group, showing that tennis has the same effect on humeri all around the world. Thus, Jones et al. got it right 25 years ago just by looking at plain x-rays.

Bad news for MDs: Playing golf is no good for your bones

Dorado et al. (University of Gran Canaria), taking advantage of their local environment, performed whole-body DXA

scans in a group of 15 professional golfers¹⁷. Their disappointing finding was that long-term professional golf participation is not associated with significant increments in regional or whole-body bone mass as compared to sedentary controls. Apparently, the stresses that arise during golf playing are not large enough to elicit any adaptive response in bone mass (bone geometry was not measured). Whatever the explanation for this observation, it seems that from a skeletal point of view, the risks of golf playing (golfer's elbow) clearly outweigh the benefits (none).

From titin to the IOC (Jörn Rittweger)

Some biochemistry...

Have you ever heard of titin? Do not confuse it with Tintin, the Belgian comic strip character. Titin is a muscle cell protein in search of a function. It had been known for a long time that besides myosin and actin there is quite a lot of titin in the muscle cell. Well, everybody knows that myosin and actin convert chemical into mechanical energy and produce force and shortening of muscle, but what does all the titin do? Now, the functional role of titin appears to be clear, at least as far as cardiac muscle is concerned. Li et al. found that titin acts as a structure that provides passive elasticity¹⁸. It does so in a complex structure-dependent manner, unfolding only one part of the protein under physiological conditions. It maintains a buffer for unfolding and the consequent uptake of elastic energy, when the physiological range is exceeded. It remains to be shown, however, whether the titin of skeletal muscle works in a similar way.

... and some geometry

Some JMNI readers may have encountered difficulties when trying to publish morphological muscle data based on computed tomography. The reviewers sometimes argue that the 'gold standard' for muscle morphology is magnetic resonance imaging (MRI). The latter, however, is quite expensive and time-consuming. It may thus be a good idea to look for an alternative method to estimate muscle volume or muscle cross-sectional area. Esformes et al. show that ultrasonographic measurements correlate quite well with MRI measurements of the human tibialis anterior muscle volume¹⁹. Both ultrasonography and MRI yielded comparable reproducibility. Results were similar between both methods, with an error of -0.15% to 5.17%. This should hopefully convince the reviewers of your future manuscripts!

Low strains, big gains? Give me a break, if possible with coffee!

Thanks to Dr Schiessl's tireless efforts at ISMNI meetings and elsewhere, most of us have come to look at bone like an

engineer. As such bones should be adapted to the largest strains they experience. Besides the magnitude of strains, there has been a vivid debate about the role of strain rate and strain frequency. Now Srinivasan et al.,²⁰ come forth with a new and appealing factor that might influence bone formation: Strain rest!

In two animal models, the authors demonstrate that bone formation increases when the number of cycles with moderate strain magnitudes (around 650) decreases, provided a 10 second pause is maintained between the cycles. In the isolated turkey ulna-loading model, 100 cycles applied at 1 Hz had hardly any effect on periosteal bone formation. However, only 10 cycles with the same parameters except for the 10 second rest period elicited bone formation on more than 20% of the periosteal surface.

Similar results were obtained in the noninvasive mouse tibia loading model. Again, low strain loading for 5 days with a 10 second rest period induced a significantly greater periosteal bone formation rate than the same regimen without rest but with a greater number of strain cycles! In fact, the bone formation rate produced by the 'rest regimen' was only slightly lower (not significantly different) than that induced by a regimen with peak strain twice as high but without rest.

Less can be more, as we know already from Umemura's experiments in rats a few years ago²¹. These studies had shown that a small number of jumps per day are (almost) as effective for bone hypertrophy as a large number of jumps²¹. Together with the very interesting findings of Srinivasan et al. it may become necessary to revisit the exercise regimens recommended for elderly patients. Moreover, such results are interesting from a mechanistic view. One of the unsolved problems regarding the fluid-flow theory of mechanotransduction is that once the mechanical strain has squeezed the fluid out of the bone, it would probably take several seconds for it to return. Instead of tinkering with this theoretical problem, let's turn it into a practical advantage: Get more bone while resting! Or, as the old Romans said, *Natura parendi vincitur*, a good theory is a most practical thing.

Another proposal for cheating Mother Nature comes from the field of exercise and sports physiology (from where else?). It has been observed that many athletes ingest defizzed Coke during the end phase of competitions. Cox et al.²² have replicated this under laboratory conditions. They indeed found that caffeine enhances muscular power output during the final stage of a two hour ride at 70% of the maximum sustained power output. A dose of 6 mg caffeine per kg body mass increased power output significantly by about 3%, whereas the extra carbohydrates had no effect. The authors failed, however, to find a metabolic reason for the enhanced power output. They suggest 'central nervous effects' as the most likely explanation.

So, what about a coffee-break at this point, preferably one without sugar? Don't overdo it, however. If you exceed the urinary caffeine levels allowed by the International Olympic Committee (12 mg/l), you may lose your job if one of those

surprise doping testers shows up (depending on what your job is). There is no need to be too afraid either. Those urinary caffeine levels are expected after the consumption of 12 cups of coffee or 21 liters of Coke. Cheers!

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