

What is new in neuro-musculoskeletal interactions?

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Arm development: pitfalls and progress

Studying muscle-bone interaction during the development of upper extremities is a daunting task, because ‘muscle and bone are inextricably linked by common genes and a shared loading environment’, as Daly et al. point out¹. They nevertheless set out to extricate the inextricable by examining people who are very popular with bone scientists: female tennis players. In contrast to most earlier such studies they did not only look at the size, mass and geometry of the humerus, but also at the muscle size of both upper arms. They found that muscle cross-sectional area was 6.7% larger in the playing arm and that similar differences between arms were present in ‘bone traits’. Yet, the difference in muscle size between playing and non-playing arms did not correlate that well with the difference in ‘bone traits’, with r^2 values just between 0.12 and 0.16. Does this mean that differences in muscle size explain only 12 to 16% of differences in bone mass, size, and geometry, as is the main conclusion of this paper? Nope. What the authors forgot is that measurement errors quickly add up when you try to quantify differences. A 1% error is good for measuring absolute values. However, when you subtract two measures you add the errors while making your endpoints small (e.g., a 6.7% difference for muscle size in this case). Thus, the signal to noise ratio worsens dramatically. When you correlate two such imprecise differences, as was done in this study, the variability in your results will be

explained more by measurement errors than by physiology.

If you want to know what attention to detail is you should rather check out two of Chris Ruff’s recent papers^{2,3}. They have a combined length of 39 pages and contain more insights in the methods section alone than the average paper has between title and acknowledgements. Ruff re-examined humerus and femur X-rays from 20 participants of the ‘historical’ Denver Growth Study (that ran from 1927 to 1967), in which healthy children had undergone yearly radiography between the ages of 6 months and 19 years. Probably the most interesting new finding in this study is that growth in humerus strength (section modulus) slows down considerably when children start to walk, whereas the increase in femur strength speeds up at the same time. Changes in muscle size, as estimated from the X-rays, were a strong predictor of changes in humerus strength in boys, but less so in girls.

Breaking arms: are girls better soccer players?

Children and adolescents have a high incidence of upper extremity fractures. Does prolonged television viewing protect against such fractures? ‘Of course not’, readers of Ma and Jones’s case-control study on the topic will answer⁴. Television viewing (including videos and computer games) had the dose-dependent effect of increasing the incidence of upper extremity fractures. This was admittedly a simple question, as no study has ever had anything good to say about television viewing. So here is a trickier one: is sports activity protective against upper extremity fractures? The answer is ‘yes’ for girls and ‘no’ for boys. For example, regular soccer playing decreases fracture risk by 48% in girls, but increases it by 55% in boys. The authors hypothesize that this gender discordance is explained by ‘different approaches to sport’. Interestingly, metacarpal cortical thickness and bone density measurements at various locations (lumbar spine, hip, total body) did nothing to ‘explain’ fractures at the upper extremity, even though the same authors had previously used the same data to show that bone density and metacarpal index were independently associated with wrist and forearm fractures⁵. They do not elaborate on this discrepancy, but conclude that bone-independent factors are likely to influence fracture incidence.

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One of these bone-independent factors might be landing technique. Lo et al. show that a brief instructional intervention (containing advice such as ‘reduce your elbow extension speed prior to hand-ground impact’) reduced the average impact forces of a forward fall on the hand by 18%⁶. One might argue that the sort of advice given in this study may not be helpful for everyone. Yet, Lo et al. have a comforting message also for people who are not sure how to reduce their elbow extension speed prior to hand-ground impact. Simply falling a number of times also decreases the impact force on the wrist in the long run, presumably because you learn from experience.

Sways, falls, and sex hormones

Decreasing the impact forces when the body hits the ground is one strategy to prevent fractures. Not falling is possibly an even better strategy. Tests of balance and functional mobility are therefore becoming more frequent ingredients of clinical bone studies. In one of these, Liu-Ambrose et al. ask the question whether postural sway and weaker quadriceps strength are overlooked determinants of fracture risk⁷. The reason why they ask this is that they had performed a case-control study, in which 21 women (age 65 to 75 years) with a lumbar spine density t-score of less than -2.5 were matched to 21 women with a t-score above -1. The group with low bone density had lower quadriceps strength and fewer points on a balance score. Thus, low BMD was associated with more swaying, which may mean a higher risk of falls.

The next question therefore is: does balance get better with BMD-increasing therapy? Uusi-Rasi et al. actually investigated this question in a randomized controlled trial on 164 early postmenopausal women, and the answer is: No⁸. Five mg of daily alendronate had no effect on postural sway. Neither had weight-bearing jumping exercise nor hormone replacement therapy, which was investigated in a separate study⁹.

Swaying and falling obviously is not limited to women. In a study of 1,040 elderly men, Szulc et al. observed that those with low testosterone levels had impaired static and dynamic balance and a higher risk of falls¹⁰. This was an observational study, so it was not tested whether androgen replacement changed the incidence of falls.

How to overcome obstacles: biomechanical advice

Imagine you are given the task to lift a 15 kg load that is placed behind a 81 cm high obstacle. You bend over the little wall and then what? Do you use both hands or one hand? Kingma and van Dieën suggest that you use one hand, while the other gives support by leaning on the obstacle¹¹. In a study on 10 healthy young men, they found that this technique decreases the average compression force at the L5-S1 joint by about 30%. However, even with optimal technique, the forces at that joint were still about 6 times body weight.

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Recommended reading

Out of one journal, is it allowed to advertise for a different one? Well, if not, who cares as only a joke that the censor (or the Editor) understands must be forbidden (Heinrich Heine). Recommended reading, as one might also say, is the Journal of Biomechanics of October 2003. It covers a number of new (and even interesting) ideas and findings around bone and its adaptation(s). One of these addresses a ‘Third Bone Space’: the bone marrow. As Currey points out in this issue¹², the hollowness of bones is – although found in most long bones – poorly understood. A study by Qin et al. in the avian ulna model suggests that there might possibly be a physiological role to it¹³. The authors have subjected the isolated, but tightened, diaphysis to hydraulic oscillations with 60 mmHg amplitude. According to the authors, such pressure is within the physiological range of muscular activity, but slightly above the marrow’s blood pressure. Interestingly, only 10 minutes of this 20 Hz vibration yielded an increase in bone mass by 18.3% – despite the immobilization which in the non-vibrated turkeys led to a decrease of 5.7%. The newly formed bone was mainly found on the periosteal, and only to a lesser extent on the endocortical surface. Also, marrow vibration reduced the formation of cortical porosity. Unfortunately, there seems to be some confusion (or is it just lack of clearness?) in the distinction between pressure gradient and flow (they are related by hydraulic resistance, and that was not measured). But anyway, the provided evidence makes a strong point in support of a contribution of cortical fluid flow to the bone’s adaptive response.

Training or not training, that is the question

Reeves et al. report in detail about the effects of resistance training in elderly humans¹⁴. It has been known since long that the muscle is as trainable in old as in young age, as impressively shown by Fiatarone more than 10 years ago¹⁵. Many other studies have found that with outcome measures such as isometric or isokinetic torque, muscle mass and its anatomical cross-section increase. Making use of 3.5 pages of methods (in small print) the new study by Reeves et al. shows that the muscle-specific force (force per physiological cross-section) increases as a consequence of training. Moreover, it was found that after 14 weeks of training, the nervous capacity to activate the muscles was also increased. It should be said here that usually, older people have a decreased activation capacity. Given the good adaptability of muscle to training even in old age, one might believe that processes in the nervous system play an important role in the age-related decline of physical capacity.

How long do training benefits stay? Formerly, it was thought that they fade away quickly. Now, we learn from a study published by Hauer et al. that this does not have to be

true¹⁶. In patients with an injurious fall (mean age 84 years), the effects of a rehabilitation program which comprised progressive resistance training were still present two years after the program had ended: leg force was still greater than on admission to the program, and physical performance as assessed by the chair rising test was still better in the training group than in the control group. These findings are even more surprising because there seemed to be no difference in physical activity between the groups, which might have helped to preserve the training effects. Definitely, these long-lasting benefits will impact on calculations of cost effectiveness of training interventions in the elderly.

So, why not stop reading here and do some exercise yourself? Are you afraid of the adverse effects of exercise? Then a study of Flakoll et al. may offer a remedy¹⁷. In a placebo controlled, double blind study it was found that US marine recruits benefit from ingesting just 10 grams of protein post-exercise. The protein group had a decreased number of medical visits (-33%), fewer muscle and joint problems (-37%), fewer infections (-28%), and was much less prone to heat exhaustion (-83%). It has to be said that the training program of these recruits lasted for 54 days and was quite hard. Hence, it is not clear how far these results apply to older people or training that is less strenuous.

That bone loss starts on the second (or even first) day of immobilization is suggested by a recent bed rest study¹⁸. Urinary Ca⁺⁺ excretion increased as early as the first (or second) day of bed rest, and so did urinary excretion of the resorption markers NTX and CTX. Interestingly, the bone formation markers, type I procollagen (PICP) and the bone alkaline phosphatase (BAP) remained unchanged over the 6-day course. It is unnecessary to say that NTX, CTX and PICP are not entirely specific to bone metabolism, but rather to collagen turnover. But the sequence of events, with an increase in Ca⁺⁺ excretion first and type I collagen breakdown thereafter strongly suggest that, indeed, osteoclastic activity was fostered within the first 24 hours of bed rest. This period, however, is too short to activate, recruit and differentiate osteoclast progenitor cells. The main cause of bone loss in disuse, however, is the emergence of new resorption sites, necessarily encompassing such activation. Hence, whether the initial changes in Ca⁺⁺ and collagen marker excretion can predict long-term bone loss still needs to be shown.

How it feels to get old

Is it not nice that bone can even benefit from a pause? As reported in an earlier JMNI issue²⁰, the same strain elicits a greater osteogenic response with a rest within the strain cycles²¹. Now, the authors show that this is also true in senescent mice²². In 21-month-old animals they found that bone formation could be stimulated twice as much when a 10 second rest was inserted between low (~800 microstrain endocortical and 1600 microstrain periosteal) strain cycles. Bone formation was non-significantly further increased by doubling the strain and by extending the rest period to 20 seconds, but

NOT by increasing the number of strain cycles. Can we transfer these results into therapeutic regimens in humans? Well, the high strains (>800 microstrain) may be difficult to achieve in the elderly. But then, in those, we usually want to prevent bone loss. And it is not for sure, that the initiation of remodeling follows exactly the same rules as modeling.

Does the 'mechanostat' fail at old age? Yes, many people would say, and as any other thing does disrupt with age, how could bone's adaptation not? A very nice study published by Stenderup et al. sheds some light on that question¹⁹. The authors went right to the hot spot: the marrow stroma cells (again the marrow!). In primary cell cultures from young (~25 years) and old (~75 years) it was found that the maximum number of stroma cell population doublings (Hayflick limit) decreases from 40 in the young to 20 in the aged. During early culture passages, no donor age-related difference was found in cellular senescence markers and telomere restriction fragment length. Likewise, no difference was found in the capacity of *in vitro* or *in vivo* bone formation, or to differentiate into adipocyte lineage. The authors conclude that 'aging is associated with decreased proliferative capacity of osteoprogenitor cells'. Maybe the authors could have stressed the positive message in their findings a bit more. Firstly, osteoprogenitor cells appear to function still reasonably well at age 75. And secondly, when compared to age 25, you still have half way to go with your Hayflick limit. Hence, there seems to be still some proliferative response possible at age 125 and above. Personally, I would love to experience that in myself.

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