J Musculoskelet Neuronal Interact 2005; 5(4):393-396

Hylonome

Recent Literature Review

What is new in neuro-musculoskeletal interactions?

F. Rauch[1] and J. Rittweger[2]

[1]Genetics Unit, Shriners Hospital for Children, Montreal, Canada,
[2]Department of Exercise & Sports Science, MMU at Cheshire, Alsager, Chesire, UK

Frank Rauch

Hip Science

Clinical bone research is largely equipment-driven. We are interested in things that we can measure rather than measuring things that we are interested in. So, to expand our interests, we need new machines (which is costly), or some clever additions to the machines that we already have (which is more palatable to our budget administrators).

Tom Beck's hip structure analysis software is such a clever addition to DXA. It can analyze regular DXA hip scans and churns out a number of structural measures, such as bone diameter, cortical thickness and section modulus (a measure of bending strength) at various sites of the proximal femur. This relatively simple program has put the muscle-bone unit on the radar screen of many clinical researchers.

Petit and co-workers, for example, have used hip structure analysis to dispel concerns that proximal femur bone geometry might not be appropriately adapted to lean body mass in overweight children and adolescents[1]. They studied young people between 4 and 20 years of age and found that overweight subjects had even a higher section modulus at the femoral neck and shaft than controls with normal weight. This difference between the two groups disappeared when lean body mass (an indicator of muscle mass) was taken into account. It thus looks like moving around some extra body weight is a kind of load-bearing exercise for the muscle system, which in turn increases the strength of the proximal femur.

The authors have no conflict of interest.

Corresponding authors: Frank Rauch, Genetics Unit, Shriners Hospital for Children, 1529 Cedar Avenue, Montreal, Qc H3G 1A6, Canada
E-mail: frauch@shriners.mcgill.ca

Jörn Rittweger, Reader in Human Physiology, Dept. of Exercise & Sports Science, MMU at Cheshire, Hassal Road, Alsager, Cheshire, ST7 2HL, UK
E-mail: j.rittweger@mmu.ac.uk

Accepted 15 September 2005

While kids with high fat mass seem to be OK with regard to their proximal femurs, the same can not be said of elderly men with low muscle mass[2]. In a large group of subjects from 50 to 85 years of age, Szulc et al. found that low 'relative appendicular skeletal muscle mass' (muscle mass adjusted for height) was associated with narrower bones and thinner cortices, which resulted in lower bending strength. Possibly more surprising is their additional observation that low lean body mass was correlated with impaired balance and an increased risk of falls. Thus, it appears that the same muscle-bone relationships hold true for overweight kids and for elderly men. Unfortunately for the men, these relationships work to their disadvantage.

Now that we have dealt with overweight youngsters and elderly men, why not have a look at the hips of young women? Nikander and co-workers examined 255 premenopausal female athletes indulging in a mind-boggling variety of sports (volleyball, hurdling, squash-playing, soccer, speed skating, step aerobics, weight-lifting, orienteering, cross-country skiing, cycling, swimming)[3]. These activities were classified according to the type of loading they apparently produce at the hip. Subjects engaging in high-impact (e.g., volleyball) and odd-impact (e.g., squash) loading sports had the highest section modulus at the femoral neck, whereas repetitive low impact activity (e.g., swimming) had less or no effect. Now the choice is yours whether you really want to do odd-impact things just to improve the section modulus of your femoral neck.

Cracking under stress

Military training comes with a lot of dangers. Even recruits who are fortunate enough to serve in a peaceful country often face a hideous enemy: stress fractures. Valimaki et al. prospectively studied risk factors for stress fractures in male Finnish military recruits[4]. Although the study apparently met with less than exuberant enthusiasm on the part of the conscripts (only a quarter of invited subjects agreed to participate), the investigators managed to follow 179 of them for a period of 6 to 12 months. During this time, 8% of study participants suffered a stress fracture. It was found that tall height, poor physical conditioning, low hip bone mineral density, as well as high serum parathyroid hor-

mone level were risk factors. Thus, the authors came up with the hypothesis that vitamin D supplementation (to decrease serum parathyroid hormone levels) might reduce the incidence of stress fractures.

For those with a deeper interest in stress fractures, Rome et al. have compiled an exhaustive review of prevention trials[5]. Most of the interventions did not work, but the available evidence seems to suggest that shock-absorbing inserts in footwear may reduce the incidence of stress fractures. But then, only one out of four studies that tested shock absorbers found a significant effect, and that report ominously "lacked important information about trial design". Why shock absorbers should work at all is not so clear. Is it not the repetitive muscle pull rather than the ground reaction forces that lead to stress fracture? Anyway, it looks like a lot of work still needs to be done before this research will make a difference to the lives of military recruits.

Muscles and bones post-stroke

Stroke is common and so are fractures after stroke. This probably makes bone problems after stroke one of the most frequently occurring neuro-musculoskeletal disorder. So for sure there are plenty of papers about the skeletal effects of stroke in the Journal of Musculoskeletal & Neuronal Interactions? Far from it. To date, only one article about stroke patients has been published in JMNI[6].

So, if we want to learn about the latest studies on the topic, we have to turn to some of the usual suspects, Bone and Osteoporosis International. Pang et al. compared paretic and non-paretic arms in 56 subjects with chronic stroke (>1 year after the event)[7]. Using DXA they found that the paretic arm had 14% less bone mineral content and 9% less lean mass but 6% higher fat mass. Multiple regression analysis showed that lean mass and muscle force were significant predictors of bone mineral content in the paretic arm. Similar studies about the proximal femur made by the same group of authors on the same patient group yielded analogous results[7]. The authors hypothesize that muscle strengthening may turn out to be beneficial for the bones of chronic stroke patients.

Jörn Rittweger

Bone, leptin and the sympathetic nervous system

The reader of this heretic column may wonder why, so far, the interplay between leptin and the bone has been neglected – although, according to the protagonists in the field it constitutes a powerful neuro-skeletal interaction[a]. Earlier studies have shown that intracerebroventricular infusion of leptin causes bone loss in leptin-deficient and wild type mice, but not in mice that lack the leptin receptor[8]. Leptin has therefore been suggested to inhibit bone formation through a mechanism of action within the hypothalamus of mice. Gerard Karsenty's group now provides evidence that intracerebroventricular leptin, via the sympathetic nervous system, does not only hamper bone formation but also boosts bone resorption[9]. The mechanistic agents in this chain of effects were found among the usual suspects: adrenergic β_2-receptors induce the osteoblastic release of RANKL via an intracellular cascade that involves protein kinase A and ATF4, an osteoblast-specific CREB-related transcription factor. In addition to these players, 'cocaine amphetamine regulated transcript' (CART), a hypothalamic, leptin-dependent neuropeptide, seems to have an effect upon osteoblasts that is independent of and antagonising to the anti-osteogenic leptin effect via the sympathetic nervous system. Further research in this interesting area should try to substantiate its relevance to human physiology, and to unravel the central nervous hierarchy of signal transmission, as the hypothalamus is neither the direct nor the unique input to the sympathetic nervous system.

Hyperhomocysteinemia – more than just a difficult word?

The latest entry in the hit list of scientific tongue twisters is the starter in the above headline. I refrain from re-typing it and suggest the abbreviation HHC instead. As the professors in biochemistry have taught us, homocysteine is utilized for the synthesis of methionine; folate and cobalamin (Vit B12) are further compounds that are required in this step. Accordingly, plasma levels of homocysteine increase when levels of folate and/or cobalamin are low. But what does all this have to do with bone?

Well, recent evidence suggests that older people with HHC have an increased risk of hip fracture. This was found in a sub-group of the Framingham study, that glorious enterprise which was begun in 1948 in order to identify risk factors for cardiovascular (and not for musculoskeletal) diseases. But HHC was also a risk factor for hip fracture in a study of Japanese stroke patients[10,11]. Hence, as the authors of these studies conclude, an old hypothesis by McKusick may hold true, which postulates that HHC compromises the cross-linking of collagen (cf[10]). Alternatively, and no surprise to the connoisseurs of osteoporosis 'research', a reduced DXA-BMD is suspected as the villain[b]. Quite interestingly, and again based on the Framingham study, DXA BMD is indeed reduced in patients with low serum levels of cobalamin[12]. But is this relationship between low plasma cobalamin, high homocystein and hip fracture not just an observational epi-phenomenon? Is there a genuine cause-effect relationship? The answer might be: yes. At least this is suggested by a recent study[13]. In a double-blind, randomized controlled study, Sato et al. supplemented folate and mecobalamin in patients with a history of stroke. After two years of treatment, serum homocysteine levels had gone

[a] Without any involvement of the muscle.

[b] It obviously did not occur to neither authors, referees, nor readers that the two postulated mechanisms are grossly incompatible with each other.

down in the treated group, and the risk of hip fracture was reduced by 80%. Importantly, there was no group difference with regards to BMD.

It seems, however, as though HHC research has inherited the institutional blind spot from osteoporosis research. Which, of course, is the risk of falls! As it is preached from the pulpits in and around Esslingen: osteoporosis may be a risk factor for hip fractures, but its cause lies in the fall! This has not been, but ought to be, investigated in the case of HHC. Therefore, JMNI readers may wish to spell term successfully in their next grant application.

Fresh news about old muscles

In contrast, I recommend some reservation when using the word sarcopenia. This term was coined by Rosenberg in 1989[14] and literally means 'poverty of flesh' - which, as the JMNI reader will be aware of, is supposed to constitute a medical problem[c]. Undoubtedly, the decline of the musculature with age gives rise to a plethora of conditions, falls and fractures being only one of them. But is it really the reduced muscle mass which causes the problems in old age, or is deterioration of function more relevant? Runge et al. have recently reported that, in a population of 'fit' elderly, the peak jumping power may decrease by 50% between age 20 and 80 without any change in calf muscle cross-section[15]. Hence, while ageing may or may not affect muscle mass, this study suggests that the loss in muscle function rather than a loss of muscle mass is a hallmark.

All this is more than a merely academic problem. Atrophy, i.e., the muscle's response to disuse and de-training, and even more so cachexia, i.e., the disease-related loss of muscle mass, are likely contributors to the changes of the musculature in the elderly. Confusing the effects of senescence[d] with those of sedentarism and co-morbidity will most certainly entail flawed diagnostic procedures and futile therapeutic attempts.

However, there is some good progress, e.g., by the very interesting rat model described by Edström & Ulfhake[16]. The beauty of this publication lies not least in the clearness of its cybernetic concepts. In that study, sarcopenia was identified in individual, aged rats as a reduction in mass of the soleus muscle. Low soleus mass was associated with disrupted locomotion. Moreover, the concentration of nuclei in the sarcopenic soleus muscles was increased, as was the concentration of the myogenic regulatory factors MRF4, Myf-5, MyoD and Myogenin, and IGF-1 mRNA. The authors conclude that, in this model, the anabolic stimuli are expressed, but eventually ineffective. If this were true in general, then the problem of the ageing muscle would not be so much its regeneration, i.e., activation and fusion of stem cells. Rather, the findings of this study would be compatible with neurodegeneration playing a decisive role.

The loss of motor units with increasing age, i.e., the reduction of motoneurons and their muscle fibres, has been known to occur for a long time and was first been described by Petito's group in 1973[17]. In the extensor digitorum brevis muscle, this affects about 75% of all units by the age of 70. It is generally thought that for some reason the motoneurones decay first. This is in particular true of those neurones that innervate fast twitch fibres. Similar findings have been made in many non-locomotor muscles. Using the sophisticated technique of decomposition-enhanced spike-triggered averaging[18], Doherty's group has now obtained the expected results, namely a loss of motor units and a reduction in fast twitch fibres, also for the tibialis anterior muscle[19]. Again, these results do highlight the important role of neurodegeneration for the ageing muscle.

[c] And not an agro-economic or culinary one.

[d] Senescence is the irreversible biological process associated with ageing.

References

1. Petit MA, Beck TJ, Shults J, Zemel BS, Foster BJ, Leonard MB. Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents. Bone 2005; 36:568-576.
2. Szulc P, Beck TJ, Marchand F, Delmas PD. Low skeletal muscle mass is associated with poor structural parameters of bone and impaired balance in elderly men – the MINOS study. J Bone Miner Res 2005; 20:721-729.
3. Nikander R, Sievanen H, Heinonen A, Kannus P. Femoral neck structure in adult female athletes subjected to different loading modalities. J Bone Miner Res 2005; 20:520-528.
4. Valimaki VV, Alfthan H, Lehmuskallio E, Loyttyniemi E, Sahi T, Suominen H, Valimaki MJ. Risk factors for clinical stress fractures in male military recruits: a prospective cohort study. Bone 2005; 37:267-273.
5. Rome K, Handoll HH, Ashford R. Interventions for preventing and treating stress fractures and stress reactions of bone of the lower limbs in young adults. Cochrane Database Syst Rev 2005; CD000450.
6. Runge M, Rehfeld G, Schiessl H. Skeletal adaptations in hemiplegic patients. J Musculoskelet Neuronal Interact 2004; 4:191-196.
7. Pang MY, Eng JJ. Muscle strength is a determinant of bone mineral content in the hemiparetic upper extremity: implications for stroke rehabilitation. Bone 2005; 37:103-111.
8. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, Shen J, Vinson C, Ruegaer JM, Karsenty G. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell 2000; 100:197-207.
9. Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannon TW, Noda M, Clement K, Vaisse C, Karsenty G. Leptin regulation of bone resorption by the sympathetic nervous system and CART. Nature 2005; 434:514-520.

10. McLean RR, Jacques PF, Selhub J,Tucker KL, Samelson EJ, Broe KE, Hannan MT, Cupples LA, Kiel DP. Homocysteine as a predictive factor for hip fracture in older persons. N Engl J Med 2004; 350:2042-2049.
11. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Homocysteine as a predictive factor for hip fracture in stroke patients. Bone 2005; 36:721-726.
12. Tucker KL, Hannan MT, Qiao N, Jacques PF, Selhub J, Cupples LA, Kiel DP. Low plasma vitamin B12 is associated with lower BMD: the Framingham Osteoporosis Study. J Bone Miner Res 2005; 20:152-158.
13. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. JAMA 2005; 293:1082-1088.
14. Rosenberg IH. Summary comments. Am J Clin Nutr 1989; 50:1231-1233.
15. Runge M, Rittweger J, Russo CR, Schiessl H, Felsenberg D. Is muscle power output a key factor in the age-related decline in physical performance? A comparison of muscle cross-section, chair-rising test and jumping power. Clin Physiol Funct Imaging 2004; 24:335-340.
16. Edstrom E, Ulfhake B. Sarcopenia is not due to lack of regenerative drive in senescent skeletal muscle. Aging Cell 2005; 4:65-77.
17. Campbell MJ, McComas AJ, Petito F. Physiological changes in ageing muscles. J Neurol Neurosurg Psychiatry 1973; 36:174-182.
18. Boe SG, Stashuk DW, Doherty TJ. Motor unit number estimation by decomposition-enhanced spike-triggered averaging: control data, test-retest reliability, and contractile level effects. Muscle Nerve 2004; 29:693-699.
19. McNeil CJ, Doherty TJ, Stashuk DW, Rice CL. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. Muscle Nerve 2005; 31:461-467.