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Review Article

Hylonome

What is new in neuro-musculoskeletal interactions?

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

[1]Children's Hospital, University of Cologne, Cologne, Germany, [2]Institut für Physiologie, Berlin, Germany

Research with impact

Are you tired of trying to get your papers published in journals with high impact factors? Then why not try high-impact exercise for a change? Heinonen et al. tell us that this may be beneficial to your bones, at least if you are a growing girl[1]. The authors studied a group of 25 premenarcheal and 39 postmenarcheal girls aged 10 to 15 years and two corresponding control groups. The exercise groups participated in an average of 1.3 training sessions per week, which included 20 minutes of jumping exercise. After 9 months of training, lumbar spine and femoral neck BMC had increased 1.8 times as much in jumping premenarcheal girls than in controls (as estimated from the figures shown in this paper). In contrast, no difference was found between exercising and non-exercising postmenarcheal girls. The authors concluded that the high-impact exercise had a clearly 'improved' bone mass in premenarcheal but not in postmenarcheal girls. This was the expected outcome, so the conclusion is easy to accept. Right?

An observer who is less enthusiastic about exercise could object that this study may as well demonstrate a classical pitfall of pediatric bone studies: The premenarcheal exercising girls grew faster than their non-exercising controls (4.9 cm vs 4.0 cm), which may appear as a small difference at first sight. However, height is a one-dimensional variable, whereas BMC (in g) depends on bone volume and therefore is a three-dimensional parameter. The 23% difference in Δheight between the two groups therefore can be expected to result in a 86% difference in ΔBMC, assuming that the bones grow to scale (without change in shape). Thus calculated, the effect of exercise, which we all had hoped to see, has evaporated. We might try to save the game by proposing that the exercising girls grew faster because of the exercise. However, there was no indication of such an effect in the postmenarcheal exercisers who actually grew 10% less than their control group (2.0 cm vs 2.2 cm).

So our hopes rest on Fuchs et al.[2] to convincingly demonstrate that jumping increases bone mass in children. It seems that they used a somewhat more vigorous training program than Heinonen et al. They recruited 45 prepubertal children to perform 100 jumps off 61-cm boxes three times a week for 7 months. Classmates doing stretching exercises instead served as controls. The percentage increase in BMC at the femoral neck was about twice as much in jumpers as in controls and it was about 1.5 times higher at the lumbar spine. This time, the differences in ΔBMC appear to be larger than would be expected for the differences in Δheight. So it looks like proponents of jumping can lean back and celebrate (after all, it is the kids who are supposed to do the jumping).

Size differences do not only create pitfalls in pediatrics, but also occur in adults. This is often neglected in the field of bone densitometry, where size differences between adults are either 'infrequent or infrequently discussed', as was humorously remarked in a recent editorial comment[3]. Elkin et al. provide an example for the fact that size does matter also in adults. They noted that leg and total body areal bone mineral density (BMD) were lower in adults with cystic fibrosis (CF) than in age-matched controls[4]. However, CF patients were shorter than controls (171 cm vs 177 cm) and the height-adjusted values were not significantly different between the groups. Size obviously is also an important determinant of muscle force. CF patients had a lower maximal isometric quadriceps force than controls, but the difference disappeared after correction for leg muscle mass. Therefore it is concluded that the CF patients' muscles had an undisturbed force-generating capacity. Unfortunately, we are not told whether muscle force and mass were adequate for body height in these patients.

Most bone densitometric studies focus on bone mass. The implicit assumption is that heavier bones are stronger than lighter ones. However, the strength of a structure depends not only on how much material was used to build it, but also on how the material was arranged. Schoenau et al. examined the developmental changes in the relationship between bone bending strength (as reflected by section modulus) and bone mass (BMC) at the radial diaphysis[5]. The ratio between these two parameters was similar in prepubertal boys and

Corresponding authors: Frank Rauch, MD., Shriners Hospital for Children, 1529 Cedar Avenue, Mondreal, Qc H3G 1A6, Canada. E-mail: frauch@shriners.mcgill.ca Jorn Rittweger, Institute für Physiologie, Arnimallee 22, 14195 Berlin, Germany. E-mail: ritmus@zedat.fu-berlin.de

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girls. During puberty the section modulus/BMC ratio increased in boys but not in girls and this gender difference persisted until adulthood. This means that 1 g of bone mineral in a man's radial diaphysis is 'stronger' than 1 g in a woman's diaphysis. The reason is that during puberty girls add bone on the inner surface of the cortex, whereas boys add bone at the outer surface. Material which is further away from the center has a greater effect on strength than more centrally-located material.

Do you feel stressed? – Here is why

JMNI readers are familiar with the fact that the largest physiological loads on bones result from muscle contraction, but it is nevertheless interesting to realize just how large those loads are. A number of recent studies have looked into this question in various parts of the body. Choi et al. provide an electromyography-based study on muscle forces and spinal loads at the C4/C5 level[6]. Ten young men were asked to sit in a chair and their arms and upper body were strapped to a board behind the chair. A headband was worn by each subject, and the headband was connected with a rope to a fixed force transducer. The largest loads were calculated for isometric head flexion, with mean C4/C5 joint compressive forces reaching 1654 N (corresponding to more than twice the body weight of an average man).

Morris et al. went a little further down the spine to test the mechanical loads on the L4/L5 joint during rowing[7]. In 14 competitive female rowers the peak compressive force averaged 2694 N, equaling 4.6 times body weight. These individuals had a 4% higher areal BMD at L2-L4 than age-matched non-rowers, which the authors attributed to the rowing activities. Unfortunately, it was not taken into consideration that the rowers were taller, and thus the difference between the two groups could also be explained by simple size differences.

Let us leave the spine behind and consider what happens when our body meets the ground. Giddings et al. developed a finite element analysis of the calcaneus and used it to examine calcaneal loading during walking and running[8]. Peak talocalcaneal joint loads were 5.4 and 11.1 times body weight during walking (at 6 km/h) and running (at 13 km/h), respectively. One might assume that loads during the gait cycle are highest when the calcaneus hits the ground, but this is not the case. The loads on the calcaneus are severalfold higher, when the foot is 'getting ready for take-off'. The reason is that the main loads on the calcaneus result from Achilles tendon forces, which in this model reach 3.4 and 7.7 times body weight during walking and running, respectively. These calculated forces in the Achilles tendon are corroborated by non-invasive in vivo measurements[9].

What kind of strains do these forces create in the bones? If you want to study this question, you need to find volunteers with real dedication. They should be prepared to have little holes drilled into their tibial cortex and have strain-gauge staples inserted, so that their bone strains can be monitored during walking, running, cycling or other activities. This is exactly what was done in a study on six volunteers, as reported by Milgrom et al.[10] Regular walking at 5 km/h caused 840 μstrain in tension and 454 μstrain in compression at the anterior tibial midshaft. The effect of walking was considerably greater than that of cycling (271 μstrain and 291 μstrain, respectively), but less than the effect of running at 17 km/h (1378 μstrain and 1675 μstrain). The largest strains, however, were found neither in tension nor in compression, but in shear (1183 μstrain for walking, 628 μstrain for cycling and 5027 μstrain for running).

Making sense of strains - Osteocytes

Stresses strain the skeleton and osteocytes are ideally located (if not the only plausible type of cells) to sense the strains and convert them into biological responses. Wang et al. have developed an interesting model which describes the situation of cortical osteocytes[11]. Fluid is squeezed out of the lacunar-canalicular system when the bone is compressed (Fig. 1A), and is sucked in again when the compression is released (Fig. 1B). No net fluid flow occurs, so how come nutrients can get transported along the lacunar-canalicular system? Very small molecules will simply get through by diffusion, but larger ones need to be transported by convection. Wang et al. propose that as nutrient-rich fluid from the Haversian canal reaches a lacuna through the canalicular system, there is an instantaneous mixing with the nutrient-poor fluid within the lacuna (Fig. 1B). The fluid which is squeezed out of the lacuna during the next loading cycle therefore has a lower nutrient concentration than the fluid which was sucked in (compare Figs. 1B and 1C). Due to the lacunar mixing process, there is thus a net transport of nutrients. The second lacuna is reached during the next unloading step (Fig. 1D).

The transport of nutrients to osteocytes thus is a load-dependent mechanism. An interesting aspect of this model is that the strain in the bone tissue has to be large enough to transport the fluid from the Haversian canal into the first lacuna. Otherwise, the nutrients will just move back and forth in the first canaliculus. Thus, this model predicts a minimal effective strain for osteocyte nutrition. Among other things this minimal effective strain depends on the length of the canaliculi and their contents.

Two morphological studies further refine our view of osteocytes. Ardizzoni shows that osteocyte lacunae get smaller from the cement line towards the Haversian canal[12]. Along with this, the lamellae harboring the osteocytes get thinner. These observations suggest that the mechanical strength of an osteon increases from the periphery to the center, because the holes containing osteocytes are smaller.

Kamioka et al. examined the three-dimensional distribution of osteocyte processes[13]. They found that osteocytes which have just become buried in osteoid hold contact to about 6 osteoblasts, whereas an osteoblast is connected to only one osteocyte. Thus, each osteocyte seems to have its territory of

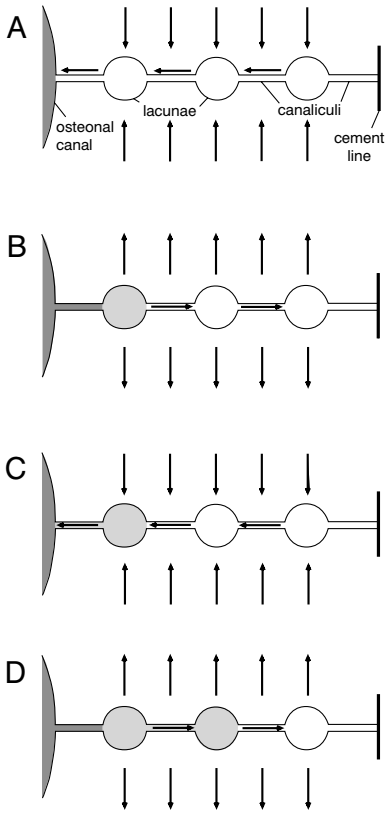

Figure 1. Schematic representation of a lacunar-canalicular system. Three lacunae containing osteocytes are arranged in series and drain into an osteonal canal, which is shown only in part, because it is much larger than a lacuna. A nutrient molecule has just newly arrived via the blood stream, achieving a high concentration in the osteonal canal. Figures A to D show nutrient transport during two loading cycles. See text for details.

osteoblasts. Those osteoblasts which are nearest to 'their' osteocyte receive the largest numbers of processes. These findings are in accordance with Marotti's hypotheses on osteocyte recruitment[14], which form the basis of a model of bone remodeling discussed in this column before[15].

Muscle: NO news

A recent review article gives us a first functional perspective of nitric oxide (NO) in the skeletal muscle[16]. During the past years, there has been quite some research in the field, but often contrasting results were obtained.

Three different types of nitric oxide synthase (NOS) are known: NOS1 (nNOS), NOS2 (iNOS), and NOS3 (eNOS), with an additional subtype (nNOSμ), which is synthesized by alternative DNA splicing in the skeletal muscle. NOS1 seems to be most important for the physiological muscle function, whereas under pathological conditions, NOS2 and NOS3 come into play. The main targets of NO are the neuromuscular endplate, the Ryanodine-receptor, cytochrome c, creatine kinase ...and many more. Interestingly, the SERCA2 (a Ca^{++}-ATPase that pumps Ca^{++} back into the sarcoplasmatic reticulum of the slow twitch fibers) is increasingly nitrated in aged rats, an effect that is probably due to NO. Moreover, NO seems to be involved in what goes wrong in patients with Duchenne's muscle dystrophy, as well as in the mdx mice, an animal model for this disease. In both cases, the muscle sarcolemm is completely devoid of NOS1, which is not the case in healthy humans or wild type mice.

As to NO's physiological function, three observations seem to be consistent. (1) NOS1 activity increases with muscle stimulation, probably triggered by intracellular Ca^{++}, (2) NO is involved in the regulation of the membrane's resting potential, and (3) NO can attenuate force production of contracting muscles, particularly in the presence of other reactive oxygen species. Thus, NO might be protective for the muscle during intensive activation. It might be fruitful in future studies to clearly distinguish between muscle force, velocity and power of contraction.

Surprise in exercise

Conventionally, exercise is thought of as a one-way road: muscles are engaged by motoneurones and this is it. Now exercise seemingly strikes back, as elucidated by two recent papers.

The first surprise comes from Bengt Saltins laboratory in Copenhagen. The authors found that after exercising one leg for 5 hours at 40% of the leg's maximum power, the active muscles released interleukin-6 (IL6), while IL6 liberation from the resting leg remained normal[17]. The observed IL6 blood levels were as high as in severe septicemia. In septicemia, however, IL6 is released by blood mononuclear cells, and it is thought to mediate immune responses. In the 5 hours exercise paradigm, the authors interpret IL6 mainly as a hormone, involved in the regulation of glucose delivery.

The second surprise in exercise is the stimulating effect of IGF1 on the hippocampal neurogenesis. In 1998, the granule layer of the hippocampus has been shown to bring up new neurones during adulthood, and even until the very end of life[18]. Given the fundamental role of the hippocampus, the first functional assumptions aimed at learning and memory[19]. Thereafter, it has been shown that the number of newly generated cells increases not only with learning, but also with exercise (treadmill running), and upon injection of IGF1.

Now, Trejo et al. show that injection of IGF1-antibodies completely blocks the effects of either exercise or administered IGF1, indicating a direct or indirect mediation of the exercise effect on hippocampal neurogenesis by IGF1[20]. Still we are lacking a clear understanding of what may be the functional significance of hippocampal neurogenesis. But the data definitely show: Exercise influences the shape of the muscles, but also of the brain.

No surprise, but a medical world record comes from the NIH, Bethesda. Dickerman et al. have DXAed the squat lifting world record holder who now besides his 469 kg world record holds a second, namely a lumbar areal BMD of 1.973 g cm-2, corresponding to a t-score of +6[21]. Unfortunately,

the authors do not report about the bone mineral content, nor about the dimensions of the vertebral body or about volumetric BMD, and the discussion focuses mainly on a 'critical value' for the compression of the intervertebral disk of some 15,000 N. The authors may have forgotten that it is not the force, but the strain that leads to a structure's failure. Otherwise, all elephants should suffer from disk herniation. Still, the observation made is highly interesting. The athlete under discussion started weightlifting at the age of 20 years, i.e. when his joint dimensions were already fixed. Increasing the loads applied, the vertebrae had no other way to adapt than by increasing volumetric BMD (which presumably is likewise high). Thus, we may face another beautiful example that not only the peripheral, but also the axial skeleton is adapted to the loads it experiences.

Motor control

Physiology is, as the Nobel-prize winner WR Hess stated, the science of the dead frog. That the living frog has got to tell us something important even in the 3rd millennium becomes clear from studies by E Bizzi's group[22]. The authors have combined micro-iontophoretic application of NMDA to the spinal cord with a computational algorithm to extract synergies in the EMG recordings of thus activated muscles. Surprisingly, the number of 'burst generators' or 'synergy units' found was much smaller than expected, indicating that the spinal cord operates with a rather restricted number of modules. Obviously, these modules are linearly superposed to produce the large motor variety observed from 'outside' the frog. Related studies in mammals indicate that this may be a general feature in "higher" species.

In a very beautiful review, the authors discuss the functional impact of their own results and those of others[23]. As discussed many times after (also in this column[24]), the spinal cord is more than a simple relay station to the commands from the brain, but rather plays an active role in the motor control. Most likely, it computes a limb representation from the peripheral input[25], which is compared to the internal model of the limb's physical properties[26] in order to compute the motor output signal necessary for a certain movement. The internal model is updated continuously, which is partly due to an adaptive process within the spinal cord, but also influenced by the brain[27].

This means no less than that motor learning takes place in the spinal cord – another revision of the general view that it is the cerebellum, which performs motor learning. Recently, a participation in motor learning has been attributed also to the motor cortex. Now two publications underscore this opinion, one based on functional MRI measurements during discriminative eyeblink conditioning[28], and a second based on Transcranial magnetic stimulation[29]. Both studies report an increased neuronal activity during the learning phase. Of course, this increase could be the mere effect of an increased motor output. However, Muellbacher et al. observed the reported changes only during learning of a ballistic, but not of an isometric task. Moreover, the evoked muscle potential had returned to normal on the follow-up, but not so the force output measured at the finger, which strongly indicates a change in the internal model – i.e. motor learning.

Very exciting and maybe significant news come from J Greenamyre's laboratory[30]. Since long, it has been speculated that Parkinson's disease may be related to the exposure to pesticides. Now, Betarbet et al. report that upon chronic infusion of rotenone, a 'natural' insecticide, rats develop most signs commonly found in patients with Parkinson's disease. These include nigro-striatal degeneration and the emergence of Lewy bodies (which do not occur in the to-date best established animal model, the MPTP-treated rat) and behavioural symptoms, such as akinesia and hunched posture. Of course, one has to be careful not to mistake the effects of rotenone infusion with the proof of rotenone as the causal factor. Rotenone is an inhibitor of the mitochondrial complex I. Other potent complex I inhibitors are naturally occurring. In any case, the present findings will help to understand Parkinson's disease, at least by establishing a new, better animal model for the disease.

Aging, falling and space flight

When discussing aging, one has to take care not to mix it up with immobilization, or the generally more sedentary life-style of the aged. We should thus attempt to separate the effects of aging and immobilization.

Kerrigan at al.[31] have compared the locomotor patterns of young adults with those of two groups of aged volunteers, one group of fallers, who had had at least two falls in the preceding 6 months, and a group of non-fallers. While both groups of the aged differed in several aspects from the young, the only consistent difference among the aged was a reduced hip extension in the fallers group. The authors interpret their observation as a 'hip tightness' – which, however, they did not measure. Alternatively, one could speculate on a reduced power of the hip extensor muscles. Weakness of the hip extensors as a cause for falls and hip fracture has already been discussed when trying to rationalize the fact that elderly Japanese women have half as many hip fractures (with half the daily Ca^{++} intake) as compared to western life-style countries[32,33]. The important difference may be the daily hip extension exercises that the Japanese get for free through their habit of seating and raising.

Immobilization in a very clear and instructive model has been investigated by Seki et al[34,35]. The authors studied neuro-muscular effects in human volunteers, who had their first three fingers immobilized for 6 weeks in a cast. Besides a reduced muscle volume and force during maximum voluntary contraction, the authors also report a reduced maximum firing rate and force per firing rate of the motor units, plus a reduced threshold of activation. Thus, immobilization does not elicit only muscular atrophy and increased muscular excitability, but clearly strikes back to the central nervous system. The good news: all changes

observed were mainly recovered from after 6 weeks.

It may have been mainly immobilization in a more complex model that was studied by LeBlanc et al. in crew-members of medium to long term space missions[36]. As expected by the reader of this Journal, the loss of lean body mass and whole body bone mineral content closely matched. A remarkable point about the article under discussion is that it reports the recovery of musculature, which seems to be accomplished after 30-60 days upon re-entry into Earth's gravitational field. Moreover, the authors found changes in MRI T2 relaxation times, that can be interpreted as signs of muscle soreness. These signs may persist as long as 40 days after the mission. This information is relevant to long-term missions with entry into another gravitational field. On Mars, there will be no doctor. Thus, effective counter-measures for muscle and bone atrophy must be developed to permit such missions. Already, we are on the way. As the authors put it: the Mir countermeasure program 'appears to show some efficacy'.

Presumably, also pharmaceutical interventions might help in this context, at least for bone, as has been shown by Lis Mosekilde and co-workers[37]. The investigators tested Alendronate (0.2, 1.0, and 2.0 mg kg-1 day-1) and Risedronate (0.1, 0.2, and 1.0 mg kg-1 day-1) in rats with the right hind leg immobilized by an elastic bandage. Both drugs prevented the bone loss in the immobilized leg in a dose-dependent manner, yielding normal BMD values and fracture loads at the highest dosages. As expected, but not understood, the bone loss after immobilization occurred mainly in the metaphyses, but not in the diaphyses. Hence the authors emphasize the necessity to investigate bone and bones site-specifically.

Another site specific study has been conveyed by Jorgensen et al[38]. The authors have investigated the bone loss occurring during the first year after stroke at the femoral neck in 40 patients. Comparing the paralyzed limb with the unimpaired limb, the authors found a loss of bone mineral on the impaired side – as the JMNI reader might have expected. Interestingly, however, the bone loss was more prominent at the inferior part than at the superior part of the paralyzed limb's femoral neck. Here, there was also a significant, negative correlation with the load applied to that leg during stance. These observations may tell us something about a shift in loading patterns after stroke. However, in order to predict the risk of fracture, which is increased after stroke, we need to consider not only the patients' bone, but also their neuro-muscular competence.

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