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Hylonome

Recent Literature Review

What is new in neuro-musculoskeletal interactions?

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Jörn Rittweger

News from the Department of Applied Technology

Does peripheral quantitative computed tomography (pQCT) really live up to the manufacturers' claims? A number of studies have yielded quite encouraging results. Lis Mosekilde's lab has shown that pQCT can be used as a strength predictor in trabecular bone samples from the human ilium[1]. It has also been shown that fracture load correlates very well with the 'bone strength index' (the density-weighted section modulus) in cortical bones of rats and humans[2,3]. In addition, the bone strength index correlates well with bending stiffness of human long bone diaphyses[2]. Now, Martin et al. show that in rabbit humeri the section modulus does not only correlate with bending stiffness, but also that it measures this parameter with high accuracy when adjustments based on structure theory transformation are made[4]. Despite the fact that strains in that study were measured only in one dimension (three dimensions would have been desirable) excellent results were obtained, with an r^2 value of 0.96 and an accuracy error of only 3%.

Vitamin D, analogues, PTH, muscle, falls and fractures

Psychoanalysis is the disorder that mistakes itself for its own cure.
(Jean Paul Sartre)

The 2004 shooting star in musculoskeletal research appears to be vitamin D. The current interest of the vitamin D community is less on bone but rather focuses on the question of what vitamin D and its analogues do for muscle and how this may relate to the risk of falls and fractures.

It has been known for a long time that low serum levels of vitamin D go along with an increased rate of falls in the elderly[5]. On the cellular level, vitamin D has been shown to enhance the influx of Ca^{++}[6], which may facilitate muscular contraction. So we have a statistical association between vitamin D and falls, and we have some plausible mechanistic explanations, but we still cannot be sure that the relationship between Vitamin D and falls is really a cause-and-effect story.

Randomized clinical trials should shed some light on this matter. Administration of vitamin D to frail elderly people should improve their muscle function and consequently reduce their risk to fall and to fracture. Indeed, a number of studies support that notion. In a meta-analysis of five trials[7-11], Bischoff-Ferrari et al. convincingly demonstrate that vitamin D or its analogues can reduce the risk of falls in frail elderly people by 22%[12]. Another recent study shows that oral or subcutaneous application of vitamin D reduces the risk of falls by about 50% in women who had had a hip fracture[13]. Other new studies point in the same direction[14,15]. Thus, may we lean back and contently accept Hypothesis 1 (see Figure 1)? Or is the story more complicated and hence more rewarding for the academic clinician?

In a study performed in 243 former hospital patients deemed to be frail, neither vitamin D nor exercise appeared to have any effect on performance (walking speed, among others), self-rated health (physical component of the SF36) or on the risk of falls[16]. As far as the exercise is concerned this is not much of a surprise, as it was limited to knee extension at a load equivalent to ~50% of the 1-repetition maximum[(1)]. The 6-month intervention did not bring about any changes in the isometric knee extension torque but resulted in a significant number of musculoskeletal injuries in the exercise group.

The vitamin D arm of the study probably contains more relevant information. Likewise, no effect was observed on the outcome parameters. Interestingly, this study did not provide any calcium supplementation. A recent publication by Dukas et al.

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(1) Current recommendations for resistive training are 60-80% of the 1-repetition maximum.

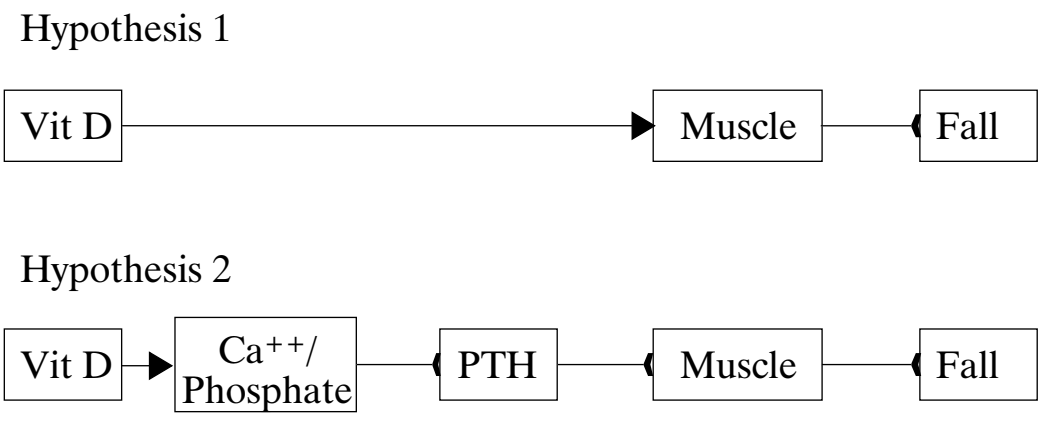

Figure 1. Schematic representation of two alternative hypotheses on the mechanism of action of vitamin D and analogues (Vit D). Regular arrowheads indicate facilitating influences, inverted arrowheads indicate counteractions. For explanation see text.

shows that alfacalcidol, a vitamin D analogue, reduces the risk of falling only in the frail elderly with a calcium intake below 512 mg per day[11]. These authors also report that the benefits could be observed only in patients with poor renal function[17]. Moreover, the authors identify a compromised renal function as an independent risk factor of falls in the frail elderly[18].

All of these findings are not compatible with a direct effect of vitamin D hormone alone, but rather suggest indirect effects or an interaction with other mechanisms. Could it be parathyroid hormone (PTH) that is doing it all (see Hypothesis 2 of Figure 1)? Sambrook et al. suggest that serum PTH predicts the time to fall independently of Vitamin D status[19]. In that study, PTH serum levels were correlated with static balance, chair rising time and quadriceps 'strength'. After the measure of static balance, PTH was the strongest predictor of falls in the study population of the frail elderly. In contrast, vitamin D levels were not predictive at all after correcting for age, incontinence, and illness severity. Future research will hopefully show whether the latter finding is (1) a statistical artifact caused by one turn too many in sophisticated adjustment acrobatics, (2) due to the fact that it is 1,25 OH_2-Vitamin D (not measured in the study) rather than 25 OH-Vitamin D (which was measured) that is biologically relevant, or (3) a sign that PTH really matters for muscle.

PTH is now approved for the treatment of osteoporosis and is therefore supposed to reduce fracture risk. Unfortunately, the risk of falls was not assessed in the drug approval study for teriparatide (recombinant human PTH)[20]. It is interesting to note that in that study PTH reduced the risk of vertebral fractures (which usually occur without a fall) by two-thirds, but the risk of non-vertebral fractures (usually caused by a fall) only by one-third. Falls, however, do not only cause fractures but compromise the daily activities of many elderly and are one of the leading causes for admission to a nursing home. It is therefore of more than just academic interest to find out whether there is indeed a strong influence of PTH on muscle and on the risk of falling in the elderly.

Frank Rauch

More on vitamin D: Also great for swimming

As Jörn Rittweger's thoughtful comments have already highlighted above, vitamin D still is a hot topic. More than 80 years after its discovery, new vitamin D actions keep popping up. In one of the latest studies on the topic we learn that vitamin D is "a key regulator of swimming behavior", to paraphrase the prevailing jargon of molecular biology journals.

Vitamin D actions are mediated by the vitamin D receptor, which is not only present in the gut and bone, but also in the brain, spinal cord and muscle. It is to no one's surprise that mice lacking the vitamin D receptor develop rickets[21]. It is possibly less expected that these mice also have a hard time swimming[22]. Vitamin D receptor knock-out mice swim predominantly in a vertical position, have catatonic-like upper limb spasms, and "demonstrate frequent sinking". "No wonder", you may interject, "don't these vitamin D receptor knock-out mice have alopecia, and therefore are at a disadvantage compared to their normal and furry littermates?" Indeed they do have alopecia, but Kalueff et al. accounted for that by shaving the controls! At the end of all this careful experimentation, the authors arrive at the somewhat underwhelming conclusion that the swimming problems in the knock-out mice are probably an unspecific effect of hypocalcemia, because serum calcium levels remain somewhat low in the knock-out mice even when they receive a high calcium diet. Thus, it is impossible to separate the effects of direct vitamin D action on brain, nerves and muscles from the indirect effects caused by hypocalcemia (and the inevitable secondary hyperparathyroidism associated with it).

The lost bone - regrown in muscle

For experts of metabolic bone disorders, "bone loss" usually is an insidious process that requires sophisticated methods for detection. In contrast, surgical specialists are often

confronted with bone loss of a less subtle nature: the destruction of a piece of bone, for example, through trauma or tumor. When the piece of missing bone is too large for natural healing to occur, a critical size defect is said to be present. It would obviously be practical if a patient could re-grow the missing piece by him- or herself. And that is where modern biotechnology comes in to provide some new forms of musculoskeletal interactions.

Warnke et al. describe a patient who had lost most of his mandible to a tumor[23]. To produce a new mandible, they used a small titanium mesh cage that was shaped like the missing mandible and filled it with bone mineral blocks that were covered with bone morphogenetic protein 7 and the patient's own bone marrow cells. This was implanted into the latissimus dorsi muscle, where a new bone grew in the form of a mandible. The new bone, together with its vascular supply, was transplanted as a free bone-muscle flap to repair the mandibular defect.

Another avenue to convert the latissimus dorsi muscle into a bone-growing incubator was explored by Abdelaal et al.[24]. An adenovirus expressing bone morphogenetic protein 9 was injected into the latissimus dorsi of nude rats to cause bony differentiation of that muscle. Two weeks later, bone tissue had developed that was still soft enough to be moldable and thus might be used for reconstructive applications.

And finally, primary muscle-derived stem cells can be genetically engineered to express bone morphogenetic protein 4[25]. These cells can then be seeded on collagen sponges and implanted directly into a critical size defect where they stimulate callus formation.

Bone in paraplegia

Spinal cord injury is one of the most important topics in the field of neuro-musculoskeletal interactions, as bone loss following the injury often leads to fractures. Eser et al. performed a careful cross-sectional analysis in 89 men with complete para- or tetraplegia[26]. Using peripheral quantitative computed tomography, they found that femur and tibia bone mass decreased exponentially with time after injury, reaching a new steady state after 3 to 8 years. Interestingly, bone mass loss was site-dependent even in the same bone, with epiphyses losing twice as much bone as diaphyses. The sites also differed in the mechanism of bone loss: in the epiphyses, bone loss was due to a decrease in trabecular bone mineral density, whereas in the diaphyses, cortical bone mineral density remained unchanged and bone was lost through endocortical resorption. Muscle spasticity and muscle size were positively associated with the amount of bone, suggesting that spasticity helps to preserve bone[27].

Modleskey et al. used even more sophisticated technology – magnetic resonance imaging – to study trabecular bone in the distal femur and proximal tibia of 10 men with complete spinal cord injury[28]. As expected, trabeculae were reduced in number and thickness in these patients. The authors concluded that "bone microarchitecture is deteriorated" in spinal cord injury, which looks like an elegant way of saying that such patients don't have much spongy bone.

Is there anything that can be done to prevent this bone loss? This is currently studied at a number of centers, but as we learn from Goktepe et al., it is unlikely that wheelchair basketball will turn out to be the treatment of choice[29]. They compared areal bone mineral density between paraplegic elite wheelchair basketball players and paraplegic controls who did not participate in sports. Basketball players had higher areal bone mineral density at the distal radius, but not at sites below the injury level.

News from Lucy

You certainly remember Lucy, the little old lady also known as Australopithecus afarensis, who came to late fame (several million years after her death!) about 30 years ago when she was unearthed in Ethiopia. Being by far the most complete early hominid available has ensured her a high degree of scientific attention ever since. The latest attempt at understanding Lucy was undertaken by Nagano et al. who used a new approach called forward-dynamic neuromusculoskeletal 3-D computer modeling to simulate her locomotion[30]. The new thing about this modeling approach is that it starts out with neural activation patterns sent to the muscles and derives movements, forces and energy expenditure from there. These complex calculations lead to the conclusion that Lucy's locomotor system was optimized to walk at a speed of 2 km/h and that her metabolic energy expenditure was like that of today's 8-year-olds, who have about Lucy's body mass (30 kg). Not exactly stuff that medical students have to know for their exams, but it is nevertheless interesting to see how taking neuro-musculoskeletal interactions into consideration can help to understand our ancestors.

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