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Recent Literature Review

Recent Literature Review: New Studies on Bone Material, Fractures, Walking and Running

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Bone material, fractures and walking

Quality research on bone material

For those who feel uneasy with the term bone 'quality' but find it difficult to exactly say why, a recent article by Sievänen et al. offers argumentative ammunition[1]. As the authors point out forcefully, bone 'quality' is 'an empty term' that has been invented in order to distract people (including funding bodies) from the obvious shortcomings of DXA scans – they just explain too little of the fracture risk. The simplistic equation underlying the term 'bone quality' is: bone density+bone quality= resistance to fracture. The term bone density lumps together the densities of all levels of biological organization, and as such reflects a ragbag of things such as bone mineralization, bone geometry and bone size[2]. As 'bone quality' is defined via bone density, this term is as imprecise. Rather than trying to fill empty terms, it may be wiser to use the terms established in material sciences, and bone's structural and geometrical organization. In agreement with Sievänen et al., we should put 'bone quality' on the list of deservedly endangered terms. Personally, I have also put the article by Sievänen et al. on the students' reading list.

Speaking of bone material sciences, important progress is being made in the field of material fatigue and its repair by the remodeling sequence. In a beautiful argument, Bruce Martin brings together two hitherto unrelated observations about microcrack removal[3]. On the one hand, 'targeted' remodeling is thought to specifically remove microcracks[4]. On the other hand, bone multicellular units (BMUs) tunnel their way through compact bone always in line with the principal stress[5]. Martin demonstrates in his recent work that the radius of action of a BMU seems to be about 10 times larger than the actual radius of the tunnel that the BMUs osteoclasts drill into the bone. He describes a scenario in which osteocyte apoptosis helps osteoclasts to 'steer' towards the site of these apoptotic osteocytes. Importantly, osteocyte apoptosis is thought to occur 'ahead' of the BMU's osteocytes along the line of principal stress[6], but also within the vicinity of recent microcracks. This work represents a further step in the recognition of the mechanistic involvement of osteocyte apoptosis in the remodeling process.

Bisphosphonates are known to inhibit osteoclast activation and activity. Recent evidence suggests that they can also suppress osteocyte apoptosis in response to microcracks and therefore tamper with the remodeling cycle in yet another way[7]. It has been hypothesized for long that the density of microcracks should increase when remodeling is suppressed as a consequence of bisphosphonate treatment. Now, the first evidence is available to suggest that this seems to be the case in the clinical setting[8]. Although the authors have to admit some methodological limitations (e.g., biopsy technique), the data provided are quite suggestive that microcrack accumulation with age is aggravated in post-menopausal women who have low areal BMD and who receive alendronate. If the suspicion nourished by this recent evidence is further substantiated, then bisphosphonates may lose their current status as drugs of first choice for the long-term treatment of such patients.

Another twist in bone and estrogen research

What exactly are the interactive effects between estrogen and exercise upon bone? Some authors believe that estrogen α-receptors are essential to the skeleton's response to mechan-

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ical strains[9], but others suggest that exercise does not even have an additive effect on estrogen[10]. Now, a recent paper by Hertrampf et al. defines something like a 'third way'[11]. In a study on ovariectomized adult rats these authors found that estradiol had a protective effect on trabecular BMD that was mediated by the estrogen α-receptor. This effect was *in*dependent of exercise (running wheel *ad libitum*), whilst genistein, which is thought to act via β-receptors, was protective only when combined with exercise. Paradoxically, genistein itself reduced the animals' propensity to run. Hopefully, the authors will follow this work up to further elucidate this often confusing, but important field of investigation.

Expected and unexpected news on fracture risk

The bottom line to all our reasoning about musculoskeletal and neuronal interactions is, of course, the risk of fracture. Fracture risk increases with age, and as the world's population is ageing, an epidemic of hip fractures has been prophesized for the years to come. The effect of aging is believed to be aggravated by a secular trend towards increased fracture risk at any given age[12]. A couple of recent studies suggest that this secular trend has now been stopped or is even mildly reverted. In the latest of these reports covering the years from 1991 to 2000, the age-adjusted incidence of hip fractures decreased by 1.3% per year in women (i.e., by 13% over 10 years), but no change was observed in men[13]. Sounds like good news, at least for women, doesn't it? However, when assuming that the reason behind this trend is the combined effect of increased general awareness, pharmacological intervention and altered exercise behavior, the good news does not sound so good anymore. After all, 87% of all hip fractures do still occur, despite all the efforts made to prevent them, not to speak of the money thrown at the problem.

In case you now wonder whether self-prescribed exercise is a cheap way to prevent fractures, you might wish to peruse Michaelsson's 35 years (!) follow-up study in men[14]. Unprecedented in the rigor of its design and the length of follow-up, this study should receive quite some attention. It shows that recreational participation in exercise is by far the most powerful protective factor among the list of the usual bone health suspects (e.g., vitamin D and calcium intake, etc.). The authors think that one-third of all hip fractures could be prevented by regular organized exercise. Such a recommendation is unlikely to be taken up by the entire population, but the message of that paper is nevertheless clear. Regular physical exercise can reduce the risk of fracture by amounts that are comparable or even greater than pharmacological interventions.

Seasonal thoughts on human locomotion

After an opulent meal (Christmas is near!), can't you decide whether to go out for a walk, or whether to stretch out and have a nice read instead? Well, why not combine both and read about a study on walking[15]? You would then get to know some interesting evidence that bipedal walking evolved because it is more energy-efficient than quadrupedal walking. The greater energy-efficiency of bipedal walking when comparing species has long been known. However, in the past such benefit was not observed within one species (e.g., the chimpanzee), and it was therefore unclear whether the evolution of bipedal walking could be driven by energy efficiency. Now, Sockol et al. demonstrate the energy benefit in the chimpanzee. Rather than looking at group averages, the authors compare the metabolic cost of locomotion in individuals, and it turns out that, indeed, single individuals seem to be more efficient when walking on two rather than on four legs. Moreover, the study links the metabolic cost to biomechanical design, namely a straighter knee-hip configuration, and the longer leg in humans – factors that largely contribute to the risk of falls and hip fracture. So, if you still want a walk after your heavy meal, be aware that you have to walk longer than your chimpanzee in order to lose the same amount of weight. That is the price of being so efficient!

Weight-bearing or load-bearing, that is here the question...

More and more evidence becomes available these days in support of the 'muscle-bone hypothesis'. It is a central tenet of this 'hypothesis' that the largest forces bones experience are generated by muscle contractions and not by the body weight *per se*. Whilst body weight is unimportant to the loading of the upper limbs, it does contribute to the habitual loading of the lower extremity by providing inertial resistance to the effects of leg muscle contractions[16]. Given a mechanical (dis)advantage of the calf muscles of 1:3, theory suggests that the 'inertial' force component in the loading of the leg bones is around 25%. Interestingly, a new study now comes up with an estimate of 30% for this component[17]. The manuscript contains some very interesting material, however, a closer look at the 30% figure shows that the evidence for it is not completely convincing. This is because internal (tendon) lever arms have not been considered, and without them it is impossible to infer from external forces or torques upon internal musculoskeletal forces. Secondly, the simple equation of bone mineral content with bone strength does not take full account of the local anatomical loading patterns in the upper and lower extremity. Thus, although the present study already seems to provide a realistic estimate, it may be left to future studies to demonstrate the different effects of weight-bearing and load-bearing upon bone beyond any scientific doubt.

Frank Rauch

On simulated runs and stimulated rats

Some unusual lab animals

"Daddy, can you run faster than a Tyrannosaur?" If you are unable to answer this basic palaeobiological question from your eight-year-old, we can recommend Sellers' and Manning's

recent paper to you[18]. They built a computer model using 'evolutionary robotics' to calculate running speeds from parameters like leg length, body mass, joint range of movement and muscle mass. Warning label: Do not do this at home; this kind of computer simulation might make your laptop battery explode! It took 300 processors working in parallel and many weeks of computing to come up with the conclusion that daddy might outrun the Tyrannosaur, but on a good day only. The maximal speed of a human in this model was 7.9 meters per second, whereas the Tyrannosaur on average came slightly ahead at 8.0 meters per second. However, both humans and Tyrannosaurs were left in the dust by the agile emu (13.3 meters per second).

Running into trouble

Both the hypothetical daddy and the dinosaur from the above paragraph probably have little time to worry about the adverse health effects of running. Nevertheless, stress fractures of the tibia are a problem in many competitive runners. Sasimontonkul et al. shed some light on this topic by using an 'integrated experimental and modeling approach'[19]. The experimental part of the approach consisted of having ten men jog around in the gait lab. The modeling bit was done by feeding movement data and force plate measurements into a computer model of lower extremity anatomy that included four segments (pelvis, thigh, lower leg, foot) with 21 muscles. The computer calculated that the distal end of the tibia was simultaneously compressed and sheared posteriorly for most of the time while the foot was on the ground. The peak forces occurred during mid-stance – and not when the heel hit the ground as one might intuitively assume. Muscle forces were by far the major source of tibial compression, which reached 9 times body weight during this moderate jogging exercise. The tibial shear was only about 0.6 times body weight and was mainly due to the forward inclination of the leg relative to the external ground reaction force. The conclusion is that the superposition of peak compressive and posterior shear forces may contribute to stress fractures in the posterior aspect of the tibia. So what is a runner to do? The authors suggest that changes in running technique could potentially reduce stress fracture risk, but are somewhat tight-lipped when it comes to practical advice. Stressed out runners will have to wait for the next publication of this research group.

Do muscle bellies shape our bones?

Many articles in this journal are based on the idea that bone formation and resorption rates are determined by the local deformation of bone tissue. Bending in one direction, for example, will cause periosteal expansion in such a way that the bone will increase its resistance to this bending force. So far so good, but what about the effects of direct pressure or tension on the bone? In a recent study Carpenter and Carter start out with the observation that bones tend to be flattened at locations where muscle bellies exert pressure on the periosteum[20]. Conversely, ridges often arise where muscles, ligaments and membranes pull on bone surfaces. The authors then devised a computer model in which the speed of bone modeling on the outer bone surface is mainly determined by intracortical strains arising from functional loading, but is modified by strains that are directly applied to the periosteum. As tends to be the case with such computer simulations, the authors' initial hypothesis (at least the one stated in the paper) is confirmed. The authors propose that muscle pressure might explain why the midshaft tibia is almost universally triangular in a large variety of species, even though these animals have very different patterns of locomotion.

Strong bones vs. weak evidence

'Use it or lose it'. This succinct summary wraps up conventional wisdom in the exercise-and-bone field. Proponents of this view like to state that it is all nice and well to build a strong skeleton during youth, but afterwards you have to keep very active to maintain it in good shape. Some high-profile support for this came from a study in soccer players, in which subjects who were still actively playing had high bone density in the legs but their retired colleagues did not[21]. The authors of that study later compressed a 21-page review on the topic into the headline "the evidence that exercise during growth or adulthood reduces the risk of fragility fractures is weak"[22]. The evidence may be weak but the bones of ex-exercisers are not, at least if we believe a new study by Warden et al.[23]. These authors came up with the provocative statement 'exercise when young provides lifelong benefits to bone structure and strength'. This statement was based on their experimental study in which they directly stimulated the forearm of growing rats by external compression. The 'training' in these rats does not look particularly vigorous, as it consisted of just 21 three-minute training sessions that were applied over the course of 7 weeks. Nevertheless, the effects of the training on ulnar strength and structure were still clearly visible when these young rats had turned into old rats (92 weeks after retiring from active experimental duty). It is also interesting to note that 'exercise' during growth had a long-term effect on bone geometry and strength but not on bone mass. It obviously makes more sense for exercised bones to optimize their shape than to increase their weight. This is why bone mass (or density for that matter) is not an adequate outcome measure in exercise studies.

Growing under pressure

Apart from growing in diameter, bones of young rats grow in length. This of course is what growth plates are for. Until recently the interaction between mechanical forces and growth plate activity did not receive much attention. This is now changing. Villemure et al. remind us that growth plates are inhomogeneous[24]. As such, a uniform outside load can lead to significantly non-uniform deformations within the growth plate. Strains seem to be highest in the hypertrophic zones

where they can be 4 to 8 times higher than the strain that is applied to the entire growth plate. Interestingly, Stokes et al. report that the hypertrophic zone is the part of the growth plate that is the most responsive to mechanical loads[25]. Grover et al. examined what happens if a growth plate is subjected to compression on just one half of its surface[26]. They found that the compressed half is growing slower whereas the non-compressed half is growing faster. This may explain why severe axis deformities in children are self-perpetuating. However, small axis deformities are physiologic during childhood and 'grow out' with time. How this works remains enigmatic.

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