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Review Article

Hylonome

What is new in neuro-musculoskeletal interactions: mechanotransduction, microdamage and repair?

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Muscles and bones

The studious JMNI reader may wish to add some recent pieces of evidence to his/her portfolio regarding the 'muscle-bone' hypothesis (MBH). Starting with the potential relevance of the MBH for the ageing process, Hamrick et al. have published a study on the age related musculoskeletal decline in a new murine model[1]. Well, what actually is new is not the model (CL57BL/6 or 'Black6' mice, popular for their robustness for a long time), but rather that finally somebody looked at that model's muscles, bones and endocrine system in conjunction. In that sense, the reported findings are noteworthy, namely that muscle mass and bone mass tend to decline simultaneously, and that this decline is preceded by increasing levels of cytokines (IL-6), and decreasing levels of physical activity.

When taking applied advantage of the MBH, 'dancing for bone health' looks like an attractive alternative to what is perceived by many as stupid sweat-driving workouts in the gym. A recent study has quantified the small to moderate skeletal benefits of dancing in female non-elite dancers of different categories[2]. Because of their clever study design, the authors were able to demonstrate that these benefits (about 1% of BMC at the spine and lower body) became most prominent during and after the growth spurt, i.e. shortly before menarche. Larger effects, about 4%, were seen for the femoral neck, but these were independent of biological age.

An interventional study in pre-menopausal women, combining jumping and resistive exercise that involved either the upper and lower body or the lower body only demonstrates that bone's response to exercise is site specific[3]. As might have been expected, the spine depicted an increase in areal BMD only in those women who trained their upper body. For the MBH-adept this does not come as a surprise, but it is perhaps a good occasion to revisit a recent hypothesis. It was proposed a couple of years ago that bone's involvement in reproduction constitutes a stronger stimulus than skeletal loading[4]. According to that proposal, exercise should have little or no effect upon bone strength in women within their reproductive years. Evidence for this idea was mainly based on studies in the rat. Now, the two studies referred to above seem to disprove such a proposal for humans.

Coming back to the MBH and ageing, the reputable Riggs, Melton and Khosla consortium discuss the MBH as a 'leading theory' and explore its potential to explain the age-related bone loss[5]. Given their results, it is not too obvious why the authors are so disappointed. Actually, they have been lucky to have found something at all, as most of the variables assessed in their over simplistic approach are either questionable (e.g., whole body lean mass as an indicator of leg muscle strength) or categorically wrong (e.g., quantifying skeletal loading in terms of caloric expenditure – the MBH is not about metabolic stress!). The main quantitative argument in the article in question, however, is that 72% of the tests that the authors had invented 'in support' of the MBH had to be rejected. As is illustrated in Figure 1, such statement is entirely pointless. Therefore, the bottom line of this article is that even ill-defined approaches to the MBH may have a 'success rate' of 28%, and that some such estimates can explain up to 41% of the variation in bone strength (i.e., more than can usually be explained on the grounds of hormones*, ageing *per se*, or any other factor that I can think of at the moment). This paper may therefore be regarded as good 'ammunition' in favour of the MBH. Alternatively, it might be recommended for undergraduate classes in 'Critical Reading'.

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* Testosterone and estrogen levels were indeed measured in the study in question, but the authors obviously forgot to relate these results.

Mechanistic thoughts on mechanotransduction

'Mechanotransduction refers to the many mechanisms by which cells convert mechanical stimulus into chemical activity' (http://en.wikipedia.org). At present, exploring mechanotransduction in bone is one of the liveliest fields in all biology. Unfortunately, the way that the different schools sell their 'products' sometimes resemble trading actions in a bazaar, but good progress is made nevertheless.

One of the numerous schools claims that osteocyte viability is crucial to biological bone responses[6]. In support of this it has been demonstrated that osteocyte apoptosis (=programmed cell death) is found both with decreased loads as well as with overloads[7].

That these mechanisms are not only possible in theory, but rather can quantitatively account for the daily business of remodelling has been suggested by Hedgecock et al.[8]. In the rabbit tibial midshaft, the authors found a strong positive correlation between the density of apoptotic osteocytes with BMU activation frequency, and a negative correlation between the density of empty lacunae and activation frequency. Taken together, these data provide strong evidence for a linkage between osteocyte apoptosis and the initiation/targeting of remodelling.

New and innovative data have also been published to suggest that estrogen and selective estrogen receptor modulators elicit their action upon ostecytes (i.e., inhibition of apoptosis) by an antioxidative effect[9]. Continuation of that line of research can be of great benefit for our understanding of mechanotransduction as well as for the design of new therapeutic strategies.

Another study in this important field by Mann et al. reports on osteocyte apoptosis in hind limb unloading in the rat, and the putative role that NO-synthase (NOS) may play in this response[10]. After 2 weeks of unloading, the authors observed an increase in apoptotic osteocytes and the expected decrease in bone mass, but no change in the expression of NOS. After re-loading, the fraction of apoptotic osteocytes returned to normal, and NOS expression was enhanced. Hence, this study does not support the idea of a straightforward link between NO-production, bone adaptation and osteocyte apoptosis.

Another school in our bazaar proclaims that interstitial fluid flow (IFF) is essential. IFF is thought to be a function of pressure gradients between the marrow cavity and the periosteum. It is suggested that IFF engenders signals within bone cells by interstitial fluid shear stress. Two little pieces of evidence in this theoretical mosaic have now been added. In a straightforward study, Stevens et al. demonstrated that IFF is indeed affected by such pressure gradients, seemingly in a parametric way[11]. As a secondary outcome of that study, the authors conclude that hypoxia within bone cells does not seem to be crucially involved in the process of mechanotransduction. The second piece of evidence by Zhang et al. implies that whole bone loading leads to fluctuations in intramedullary pressure[12]. Actually, that does not come as much of a surprise, and the authors are wise enough not to make any judgement as to the differential roles of intramedullary pressure versus bone strain for mechanotransduction.

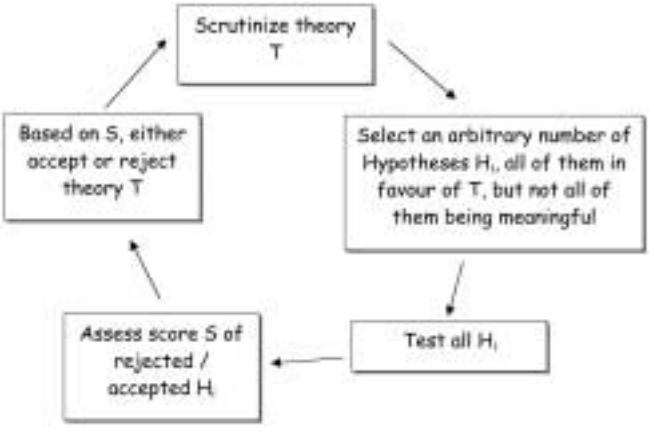

Figure 1. Exemplification of a "smart" scientific jugglery (related to the *Hysteron Proteron* in logics). Formulation of the specific hypotheses Hi is an arbitrary act by the investigator. Therefore, the set of hypotheses rejected is dependent on the available data, but also on his capabilities and intentions. Hence, the relation of accepted / rejected H_is is completely irrelevant as to the validity of the scrutinized theory T. In simple terms: hundreds of ill-formulated, rejected hypotheses cannot disprove a theory, but a single well-formulated hypothesis that has to be rejected can.

This raises an important issue, namely whether the many, many theories of mechanotransduction are to be regarded as alternatives, or do they describe mechanistic steps in an intricate physiological process? In more simplistic terms, do bones adapt to the sum of the influences of apoptosis, fluid flow, intramedullary pressure, etc.? Or do the different factors work together like the ingenious machinery of a vacuum cleaner? I think that the latter should be assumed, not least because, as Harold Frost has pointed out, the way that bone adapts to compressive, tensile and bending loads are hard to explain by a single mechanotransductive mechanism. As a remedy, he proposed a 'three-way' rule which takes into account local strains as well as whole bone strains[13]. While one may debate that three-way rule, it seems very likely that there will be several factors involved, each signaling a different aspect of bone's mechanical usage. Hopefully, this 'old knowledge' will not be forgotten when addressing the fundamental question of mechanotransduction.

Microdamage and repair

Further progress has been made recently as to how material fatigue in bone emerges and is repaired. As discussed in the past[14], linear microcracks (bad for you), which when compared to diffuse microdamage (not that bad) have a reduced capacity to absorb fracture-energy, appear to become more frequent with advancing age[15]. At that time, one could think that this is merely an effect of the bone's material age. Not necessarily, suggests a recent follow-up by the same authors[16]. The occurrence of the two types of dam-

age was related to certain microstructural compartments, with the linear microcracks prevailing in interstitial bone. This may have important clinical implications. Assuming that exercise increases targeted remodelling (and thus microdamage repair), the fraction of interstitial bone at any age would be increased by exercise. As it appears now, interstitial bone (i.e., the bone tissue in between osteons) seems to be particularly prone to fracture. Although purely speculative at the moment, this effect could lead to an increased risk of ostoeporotic fractures by exercise[17] – a notion that seems to be against the current scientific trend.

In an elegant study, Waldorf et al. demonstrate that, at least in the Fisher Brown rat, the repair of microdamage is hampered by age[18]. To do this, the authors have developed a new model to fatigue-load trabecular bone in the distal femur. Loading produced comparable microcrack densities in mature (8 months) and old (24 months) rats. However, after 35 days the microdamage seemed to be completely repaired in the mature, but not in the old animals, suggesting that repair is either incomplete or delayed. As a side-observation, bone volume fraction increased in response to loading in the young, but decreased in the old animals, potentially implying that remodelling led to a loss of trabeculae. Readers will be looking forward to more research in this highly topical field.

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