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Mini-review Article

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Ten years muscle-bone hypothesis: What have we learned so far? -Almost a Festschrift-

J. Rittweger

Institute for Biomedical Research into Human Movement, Manchester Metropolitan University, Cheshire, United Kingdom

Abstract

The importance of mechanical stimuli for bone is widely appreciated. Mechanostat theory proposes a negative feedback system to explain the adaptation of bone by homeostatic control of peak strains. However, no assumption is made as to which forces cause these strains. Biomechanical analyses suggest that the largest forces emerge from muscle contractions, rather than from body weight *per se*. Hence, the idea of a 'muscle-bone' unit emerged ten years ago, proposing that bones adapt to muscle strength. This muscle-bone hypothesis is well able to account for the accrual of bone mass and strength during childhood, and also to explain why certain types of exercise are able to prevent bone loss during immobilization. However, the hypothesis fails to explain why exercise becomes rather ineffective to increase bone strength after puberty. It is here proposed that joint size as a 'third agent' might solve the conundrum. More specifically, the assumptions are made that the peak forces determine joint size until the end of puberty, and that motor control limits joint reaction forces to critical limits during adulthood in order to prevent joint damage. Providing evidence in favour or against these conjectures will improve our understanding of the musculoskeletal system.

Keywords: Mechanostat Theory, Osteoporosis, Joint, Motor Control

Introduction: A historical perspective

It has been known for a long time that bones, as structures, are designed to fulfil their mechanical function[1,2], but only in the late 1900s did Julius Wolff, the world's first orthopaedic surgeon, recognize that bones have adaptive capability also within the individual's lifespan[3,4]. Harold Frost, another orthopaedic surgeon redefined Wolff's law, stating that structural adaptation is driven by the experienced bone strains[5,6]. Others had measured *in vivo* strains before[7], finding that they hardly ever exceed 1000 or 2000 μstrain[8], but it was for Harold Frost to propose a negative feedback system that could explain how forces affect the shape of bones[9] – the mechanostat.

While the mechanostat theory constitutes an important step, it makes no assumption about the very origin of the musculoskeletal forces. As a matter of fact, many people still believe that the principle forces would emerge from mere passive loading by our body weight. Into this vacuum of thought, Hans Schiessl injected the idea that the largest forces necessarily arise from muscle contractions, as all our muscles work against short levers, ranging from 1:2 to 1:10[10]. As a result, the internal musculoskeletal forces are 2 to 10 times larger than external forces. Others had observed correlations between muscle and bone before[11]. However, Dr. Schiessl was the first to discuss the muscle-bone unit as a functional symbiosis – in what has nowadays become a classical paper[12].

This was ten years ago. Since then, some things have changed. For instance, 'exercise & bone' has become a well-studied topic with currently more than 6,000 hits on public medline, and even available in some textbooks. However, it will probably take some more time for the scientific community to fully understand the importance of the musculature for bone. I would therefore like to take the opportunity and browse through some of the exciting musculoskeletal research carried out in the past 10 years, and to critically reflect upon its implications.

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Corresponding author: Joern Rittweger, M.D., Ph.D., Institute for Biomedical Research into Human Movement and Health, Manchester Metropolitan University, Hassall Rd, Alsager, Cheshire, ST7 2HL, UK
E-mail: j.rittweger@mmu.ac.uk

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The muscle bone unit during development

The field of paediatric bone was the first to provide substantial evidence to the muscle-bone hypothesis. As Eckhard Schönau and his team showed, muscle strength and bone strength are in close relationship to each other across the paediatric age range[13] – apparently, children's bones become adapted to the increasing muscle forces as they grow. Interestingly, this muscle-bone relationship seems to be shifted in girls after puberty[14], with women in their reproductive years having more bone mass than is explicable by their muscle strength. Crucially, muscle development seems to be ahead of bone development by a few months[15], which is strongly suggestive of muscle development playing a causal role for accrual of bone strength.

The ideas have amalgamated into a diagnostic approach to paediatric patients with reduced bone strength[16]: Whenever bone mineral content (as a surrogate of bone strength) is in proportion to muscle cross-section (as a surrogate of muscle strength), then the bone weakness is classed as secondary to the muscle weakness. In primary bone disorders, conversely, bones are weaker than expected in proportion to muscle strength, and the patient should receive a different treatment accordingly.

Well, one might ask, 'if muscles matter so much to our bones, what effects would exercise then have upon bone?'

Exercise to build stronger bones?

There is no longer any doubt that exercise can help to build stronger bones. This has been reflected by a positive paper issued by the American College of Sports Medicine[17].

These effects seem to be particularly powerful during childhood. Most intervention studies before puberty have involved some kind of callisthenics (e.g., hopping or jumping) or circuit training. These studies unanimously suggest that children who engage in such exercise have greater gains in bone strength than their more sedentary counterparts[18-20]. In children, these beneficial effects seem to persist after a year (and potentially longer) in the shafts, but not in the epiphyses[21]. Relatively little is known regarding resistive exercise but one study suggests that it may be even more effective than hopping and jumping[20].

A number of studies suggest that exercise efficacy is affected by pubertal stage, with greater efficacy during rather than before puberty[22,23]. Hence, puberty seems to offer a 'window of opportunity' to grow particularly strong bones. Other studies, however, suggest that this window of opportunity may occur just before puberty[24]. Whenever that window does occur, the opportunity passes away after puberty, as the same kind of exercise loses much of its efficacy once adolescence is reached[25].

Exercise intervention studies in young adults mostly report significant, albeit rather small benefits for bone strength[26-28]. Usually, exercises with large joint reaction forces, e.g., callisthenics or resistive exercise, have been able to elicit such small effects, whereas nothing is achieved by moderate force levels[29]. Bearing in mind a probable 'publication bias', with 'negative' results not being published, it seems fair to say that exercise intervention effects upon bone are fairly moderate in adulthood and certainly smaller than during childhood. Somewhat larger effects may be seen between the long bone shafts in athletes and their sedentary counterparts, where differences of 10-20% have been reported[30,31]. Strikingly, the differences are much smaller for the epiphyses.

Exercise can prevent disuse-related bone losses

It is well documented that, whenever muscles are not properly actuated, bone is readily lost from the disused regions. This is, for example, true for spinal cord injury[32,33] and stroke patients[34], but also in rat disuse models of tail suspension[35] or sciatic neurectomy[36]. Most likely, this is also the reason why astronauts lose bone mass and strength in their leg, but not from their arm bones[37]. The latter is considered a serious problem for long-term missions: Just imagine the caprioles of Jack Schmitt on the moon during his Apollo 17 mission (some nice footage can be found on YouTube), and think of the consequences, had he lost half his bone strength during a 1-year space travel to Mars! Therefore, effective countermeasures for bone are imperative before embarking on such trips.

Driven by the endocrinological bone paradigm of their time, past researchers first proposed hormonal treatment, among others with sex hormones to cure the 'microgravity' bone loss[38]. It turned out quickly (within a couple of decades), that such approach was flawed. In fact, in-flight substitution of vitamin-D is not only useless, but can actually be dangerous because of the risk of hypercalcaemia[39]. Thus, astronauts currently ingest less vitamin D in Space than on Earth.

Importantly, endurance exercise is not of any help, either. Luckily, the good muscle-bone message has now arrived at the responsible ears of NASA, ESA and JAXA, and resistive exercise has become a must in space – with the intent to preserve muscle and bone. The evidence for this new strategy stems from ground based research, where conventional resistive exercise[40] as well as resistive exercise in combination with whole-body vibration[41] did prevent bone loss during bed rest immobilization.

Bone losses can be recovered in healthy adults

An important issue that has not yet received much attention is the recovery of bone losses after successful rehabilitation. Harri Sievänen's 3-year longitudinal study of the patella in a young woman (I wonder who she was) with knee ligament rupture is probably the first to suggest complete or near complete recovery of such losses[42]. Recently, recovery data from astronauts have become available[43], and lo and behold!, their bones recover, too. Our own data suggest the

same thing, namely that bone losses incurred during bed rest recover well within a year or two[44]. The recovery seems to occur 'automatically', i.e., without any additional training or specific rehabilitation program. Unanimously, the 3 cited studies found an exponential time course of bone recovery, as would be expected in a feedback control system[45] such as the mechanostat. Moreover, recovery gains in each individual seem to match the prior losses[44], underlining the idea of a tight cybernetic regulation. Finally, when looking at the rate of bone gain during the recovery phase, one might be surprised by the sheer rate of bone accrual. In our study, for example, the initial accrual rate was 1.2% per month on average, and a breathtaking 4.5% per month in a single individual of the control group[44]. Importantly, this accrual rate can be compared to bone accrual during puberty, which highlights the capability of the adult skeleton to gain bone when needed.

Summary & Conclusion

In summary, musculoskeletal research of the past 10 years suggests the following:

1. During childhood, gains in muscle strength and accrual of bone mass match each other.
2. During childhood, gains in muscle strength precede accrual of bone mass.
3. During childhood, exercise can help to build stronger bones.
4. The same exercises, however, lose much of their potency after puberty.
5. Exercise effects upon bone are only weak in adults, and they are more pronounced in the diaphyses than in the epiphyses of our long bones.
6. Bone strength is readily lost in paralysis and immobilization.
7. Resistive exercise is able to prevent bone loss during immobilization.
8. In healthy adults, lost bone strength is readily recovered after successful rehabilitation.
9. Recovery of lost bone leads to equalization, but to no net gains.

Observations 1-3 and 6-8 suggest a strong guiding influence of the musculature upon bone. But why is this influence so strangely altered after puberty (observations 4 & 5) and why does recovery of lost bone stop once the original strength is restituted (observation 9)? It is hard to believe that muscular forces lose their importance within months after puberty. Is there a missing agent that could help to solve this conundrum? I am arguing here that, indeed, bringing joint size into the muscle-bone equation might reconcile observation and theory.

It is assumed by many (e.g., Harold Frost[46]) that joint size is adapted to the peak loads at the end of puberty. Currently, this is a conjecture (C1), albeit with observational backing. Although we do not know how joint size is physiologically determined, would it not occur likely that the growth plate plays a role in it? In this context, is it a mere coincidence that the effective cross-sectional areas of the physis and the joint, both containing a layer of hyaline cartilage, have the same dimensions? If indeed, there is a link between growth plate closure and joint size adaptability, then this would elegantly explain why bone becomes 'refractory' to exercise within months after puberty, as cessation of longitudinal growth and growth plate closure seems to also occur relatively abruptly[47].

If conjecture C1 holds true, and if the material properties of hyaline cartilage cannot be enhanced (for which there is no evidence), then, from a design point of view, the peak joint forces must not exceed those that the joints had adapted to at the end of puberty. Again, here is a conjecture (C2), namely that motor control limits the peak forces in order to prevent material failure. Very fortunately, a body of evidence already exists in support of this conjecture. For example, when increasing drop jump height and thereby the impulse to be generated by the musculoskeletal system (impulse = force × time), it turns out that human motor control increases the time of force generation, but not the peak joint forces[48]. Moreover, it is a truism that joint cartilage and other collagenous joint tissues are actually more at risk during our habitual physical activity than our bones – as evidenced by the clientele of orthopaedic surgeons. It seems reasonable, thus, to assume that joints impose tight limits upon the mechanical usage of our bones.

In conclusion, I see the 10th anniversary of the 'muscle-bone' hypothesis as an occasion to celebrate the progress we have made in the field of paediatric bone disease, as well as in our efforts to develop effective countermeasures for long-term space flight. However, there is no reason to rest. I have proposed here two potentially rewarding research questions (C1 & C2) in order to consolidate the muscle-bone (-joint) hypothesis. As a great physician (J. Neudert, 1.90 m) once said: "Nothing is more practical than a good theory".

Acknowledgements

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References

1. Galilei G. Discorsi e dimonstrazioni matematiche, intorno a due nuove scienze attentanti alla meccanica ed a movimenti locali. Madison: University of Wisconsin Press; 1638.
2. Thompson DA. On Growth and Form. Cambridge: Cambridge University Press; 1917.

3. Wolff J. Über die innere Architectur und ihre Bedeutung für die Frage vom Knochenwachstum. Archiv für pathologische Anatomie und Physiologie 1870;50:389.
4. Wolff J. Die Lehre von der functionellen Knochengestalt. Archiv für pathologische Anatomie und Physiologie 1899;155:256.
5. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's law: the remodeling problem. Anat Rec 1990;226:414-22.
6. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: the bone modeling problem. Anat Rec 1990;226:403-13.
7. Lanyon LE, Smith RN. Measurements of bone strain in the walking animal. Res Vet Sci. 1969;10:93-4.
8. Biewener AA, Taylor CR. Bone strain: a determinant of gait and speed? J Exp Biol 1986;123:383-400.
9. Frost HM. The mechanostat: a proposed pathogenic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 1987;2:73-85.
10. Özkaya N, Nordin M. Fundamentals of Biomechanics. New York: Springer; 1998.
11. Jones DA, Round JM, Edwards RH, Grindwood SR, Tofts PS. Size and composition of the calf and quadriceps muscles in Duchenne muscular dystrophy. A tomographic and histochemical study. J Neurol Sci 1983;60:307-22.
12. Schiessl H, Frost HM, Jee WS. Estrogen and bone-muscle strength and mass relationships. Bone 1998;22:1-6.
13. Schönau E, Werhahn E, Schiedermaier U, Mokow E, Schiessl H, Scheidhauer K, Michalk D. Influence of muscle strength on bone strength during childhood and adolescence. Horm Res 1996;45(Suppl.1):63-6.
14. Schönau E, Neu CM, Mokov E, Wassmer G, Manz F. Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. J Clin Endocrinol Metab 2000;85:1095-8.
15. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone 2004;34:771-5.
16. Schönau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res 2002;17:1095-101.
17. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. American College of Sports Medicine Position Stand: physical activity and bone health. Med Sci Sports Exerc 2004;36:1985-96.
18. MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. Pediatrics 2003;112:e447.
19. MacKelvie KJ, McKay HA, Petit MA, Moran O, Khan KM. Bone mineral response to a 7-month randomized controlled, school-based jumping intervention in 121 prepubertal boys: associations with ethnicity and body mass index. J Bone Miner Res 2002;17:834-44.
20. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD. Prospective ten-month exercise intervention in premenarcheal girls: positive effects on bone and lean mass. J Bone Miner Res 1997;12:1453-62.
21. Specker B, Binkley T, Fahrenwald N. Increased periosteal circumference remains present 12 months after an exercise intervention in preschool children. Bone 2004;35:1383-8.
22. Matthews BL, Bennell KL, McKay HA, Khan KM, Baxter-Jones AD, Mirwald RL, Wark JD. Dancing for bone health: a 3-year longitudinal study of bone mineral accrual across puberty in female non-elite dancers and controls. Osteoporos Int 2006;17:1043-54.
23. Mackelvie KJ, McKay HA, Khan KM, Crocker PR. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. J Pediatr 2001;139:501-8.
24. Bass SL. The prepubertal years: a uniquely opportune stage of growth when the skeleton is most responsive to exercise? Sports Med 2000;30:73-8.
25. Heinonen A, Sievanen H, Kannus P, Oja P, Pasanen M, Vuori I. High-impact exercise and bones of growing girls: a 9-month controlled trial. Osteoporos Int 2000;11:1010-7.
26. Bassey EJ, Ramsdale SJ. Increase in femoral bone density in young women following high-impact exercise. Osteoporos Int 1994;4:72-5.
27. Heinonen A, Kannus P, Sievanen H, Oja P, Pasanen M, Rinne M, Uusi-Rasi K, Vuori I. Randomized controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures [see comments]. Lancet 1996;348:1343-7.
28. Snow-Harter C, Bouxsein ML, Lewis BT, Carter DR, Marcus R. Effects of resistance and endurance exercise on bone mineral status of young women: a randomized exercise intervention trial. J Bone Miner Res 1992;7:761-9.
29. Sinaki M, Wahner HW, Bergstralh EJ, Hodgson SF, Offord KP, Squires RW, Swee RG, Kao PC. Three-year controlled, randomized trial of the effect of dose-specified loading and strengthening exercises on bone mineral density of spine and femur in nonathletic, physically active women. Bone 1996;19:233-44.
30. Nikander R, Sievanen H, Uusi-Rasi K, Heinonen A, Kannus P. Loading modalities and bone structures at nonweight-bearing upper extremity and weight-bearing lower extremity: a pQCT study of adult female athletes. Bone 2006;39:886-94.
31. Wilks D, Winwood K, Gilliver SF, et al. Bone mass and geometry of the tibia and the radius of Master sprinters, middle and long distance runners, race walkers, and sedentary control participants: a pQCT study. Bone 2008; (under revision).
32. Griffiths HJ, Bushueff B, Zimmerman RE.

Investigation of the loss of bone mineral in patients with spinal cord injury. Paraplegia 1976;14:207-12.
33. Eser P, Frotzler A, Zehnder Y, Knecht H, Denoth J, Schiessl H. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. Bone 2004;34:869-80.
34. Jorgensen L, Jacobsen BK. Changes in muscle mass, fat mass, and bone mineral content in the legs after stroke: a 1-year prospective study. Bone 2001;28:655-9.
35. Globus RK, Bikle DD, Morey-Holton E. Effects of simulated weightlessness on bone mineral metabolism. Endocrinology 1984;114:2264-70.
36. Zeng QQ, Jee WS, Bigornia AE, King JG Jr, D'Souza SM, Li XJ, Ma YF, Wechter WJ. Time responses of cancellous and cortical bones to sciatic neurectomy in growing female rats. Bone 1996;19:13-21.
37. Vico L, Collet P, Guignandon A, Lafage-Proust MH, Thomas T, Rehaillia M, Alexandre C. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. Lancet 2000;355:1607-11.
38. Stepaniak PC, Furst JJ, Woodward D. Anabolic steroids as a countermeasure against bone demineralization during space flight. Aviat Space Environ Med 1986;57:174.
39. Heer M, Kamps N, Biener C, Korr C, Boerger A, Zittermann A, Stehle P, Drummer C. Calcium metabolism in microgravity. Eur J Med Res 1999;4:357-60.
40. Shackelford LC, LeBlanc AD, Driscoll TB, Evans HJ, Rianon NJ, Smith SM, Spector E, Feeback DL, Lai D. Resistance exercise as a countermeasure to disuse-induced bone loss. J Appl Physiol 2004;97:119-29.
41. Rittweger J, Felsenberg D. Resistive vibration exercise prevents bone loss during 8 weeks of strict bed rest in healthy male subjects: results from the Berlin Bed Rest (BBR) study. J Bone Miner Res 2004;19(Suppl.1):1145.
42. Sievanen H, Heinonen A, Kannus P. Adaptation of bone to altered loading environment: a biomechanical approach using X-ray absorptiometric data from the patella of a young woman. Bone 1996;19:55-9.
43. Sibonga JD, Evans HJ, Sung HG, Spector ER, Lang TF, Oganov VS, Bakulin AV, Shackelford LC, LeBlanc AD. Recovery of spaceflight-induced bone loss: bone mineral density after long-duration missions as fitted with an exponential function. Bone 2007;41:973-8.
44. Rittweger J, Felsenberg D. Recovery of muscle atrophy and bone loss from 90 days bed rest: results from the LTBR study. Bone 2008; (Submitted).
45. Windlhorst U. Regulatory Principles in Physiology. In: Greger R, Windhorst U, editors. Comprehensive Human Physiology. Volume 1. Berlin: Springer; 1996. p. 21-42.
46. Frost HM. The Utah Paradigm of Skeletal Physiology. Athens: ISMNI; 2004.
47. Moss ML, Noback CR. A longitudinal study of digital epiphyseal fusion in adolescence. Anat Rec 1958;131:19-32.
48. Bobbert MF, Huijing PA, van Ingen Schenau GJ. Drop jumping. II. The influence of dropping height on the biomechanics of drop jumping. Med Sci Sports Exerc 1987;19:339-46.