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Editorial

Humble Bones
From skeletogenesis to the Utah paradigm of skeletal physiology

A tribute to the memories of Webster S.S. Jee and Harold M. Frost

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Trying to recall my memories about Webster S.S. Jee I remain stuck to the fact that he was always strongly connected to Harold M Frost. Web and Hal, while being two different personalities and scientific methodologists, always interconnected as they served the same research purpose. Web describes his first acquaintance with Hal in 1960 at the Henry Ford Hospital in Detroit, Michigan[1] with an elegant expression; he was amazed at Frost's fluorescent - labeled rib impressive biopsy samples, but also with his strong and enthusiastic personality. My opinion is that this first acquaintance played a catalytic role for the next 45 year of their cooperation. Web and Hal became and remained close friends and collaborators. I believe that all the following achievements were a result of this joint effort. They were necessary to each other, but they played different roles. Web was always a discreet companion, leaving Hal the seat of honor. In his memoriam tribute to Harold Frost, Web wrote[2] that *there are a few clinician scientists that have had such a profound impact on a scientific discipline as has Harold Frost. He advanced the basic science of skeletal biology and used to improve clinical diagnosis and treatment*. My personal view is that Web's reference to Hal equally describes both researchers as unique scientists and philosophers, but also an ideal harmonically scientific couple.

The growing musculoskeletal system in a mechanical environment

Growth is a necessary stage in the preparation of the organs in their final function in adulthood. The musculoskeletal system is likely the best example of this biological change. Bones and muscles develop harmonically and interact as a continuous adaptive mechanism to achieve enough size and strength to overcome the continuously increased needs of the growing locomotor system. As Frost emphasizes[3] "in the postnatal life, strong muscles make strong skeletal load-bearing organs, and persistently weak muscles usually make weak organs". Bone length is accelerated after birth at the growth plates and the metaphyseal region with an endochondral ossification process.

On the other hand, modeling drifts add new bone to the periosteal surfaces of the log bones finally increasing the diaphyseal diameter and cortical thickness. Muscles, tendons, ligaments, and fasciae also develop and adapt to the mechanical and non-mechanical needs, interacting with the muscular and osseous changes. According to this evidence bone development, bone adaptations and bone function co-operate in the gradual adult musculoskeletal appearance and function.

Repeated cycles of loading and uploading can produce mechanical damage. The so-called 'microdamage' in bone increases with the number of loading cycles and the size of the loads[4]. A continuous repair of the accumulated microdamages is obligatory to avoid the weakness of the bone structure which otherwise will finally result in a macro-fracture.

Muscles grow in size and strength after childhood and in adolescence following the bone growth[5] and the effect of additional non-mechanical factors, mainly the effect of hormones (growth hormone, sex hormones, etc) after puberty[6,7]. A 'muscle-bone unit' in children and adolescents can, therefore, be explained by different mechanisms[8]. The control of modeling and remodeling by mechanical factors is explained by muscle contractions and the resulting bone strains. Larger loads on bones cause bigger strains, above a modeling threshold range and finally increased bone strength. On the other hand modeling and remodeling are controlled by endocrine and other non - mechanical factors. It is calculated that only 3-10% of our postnatal bone strength is explained by non-mechanical factors[8]. In the paraplegic patient bone loss in the lower extremities is calculated above 49%[9].

The Utah Paradigm. What is the future?

Skeletal adaptation to mechanical usage is the etiological factor of bone remodeling[4]. As repeated cycles of loading and unloading develop mechanical damage, the so-called microdamages, the necessity of a counterpoint physiological mechanism of repair is obvious. This microdamage repair is initiated when load stresses exceed the microdamage threshold of bone. It is estimated that one-quarter of the fracture load can be detected by normal bone as a microdamage generator, so a mechanism of microdamage repair is mobilized in the basic multicellular units (BMUs). As a result, the damaged bone is removed and is replaced by new bone[10]. Mechanical loads on bone cause bone strains and this generates signals. This mechanism is called

mechano-transduction. This signal transmission is followed by a response of bone cells (i.e., osteocytes, osteoclasts, osteoblasts, etc.)[11]. It is important to emphasize that the largest loads on bone come from the muscles and not from the weight bearing[12].

The mechanical loads of bone can turn 'on' or 'off' on the effect of the muscular system and the response of the mechanostat[13]. This change of mechanical loads produces systematic non-mechanical processes resulting in changes of bone cells. The biological interrelationship between muscle and bone was proposed a long time ago[14]. There is also a lot of evidence (clinical and preclinical) in support of the importance of exercise in bone biology and the finding that largest loads on bone coming from muscle forces and not from body weight are effective[15].

Mechanostat is a genetically determined response to minimum effective strain with a general consequence as follows on the set-points, remodeling and modeling highways and feedback loops[16].

$$MES_{remodeling} < E_{adaptation} < MES_{modeling} << MES_{pathologic} << FX_{fracture}$$

Altering the set-points of the mechanostat with a direct cellular action of anti-catabolic and anabolic drugs we can succeed as an anti-fracture result and therefore another approach to the anti-osteoporosis therapies[17].

References

1. Jee WS. Harold M. Frost, MD, DSc. (hon) - one man's association. J Musculoskeletal Neuronal Interact J Musculoskeletal Neuronal Interact 2006;6(2):113-21.
2. Jee WS. In Memoriam Tribute to Harold M Frost, MD: 1921-2004. J Bone Miner Res 2004;2091-2092.
3. Frost HM. The Utah paradigm of skeletal physiology. Vol I Bone and Bones and Associated Problems. Chapter 3. Bone modeling by drifts, Bone size, shape, mechanical function and effects, gains, conversation 2004; International Society of Musculoskeletal and Neuronal Interactions, Hylonome Editions, Athens.
4. Hart NH, Nimphius S, Rantalainen T, Ireland A, siafarikas A, Newton RU. Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. J Musculoskeletal Neuronal Interact 2017;17(3):114-139.
5. Jee WS, Frost HM. Skeletal adaptations during growth. Triangle 1992; 31(2/3):77-88.
6. Iwaniec UT, Turner RT. Influence of body weight on bone mass, architecture and turnover. J Endocrinol 2016; 230(3):R115-30.
7. Inman VT. Functional aspects of the abductor muscles of the hip. J Bone Joint Surg Am 1947;29(3):607-19.
8. Lyritis GP, Schoenau E, Skarantavos G Osteopenic syndromes in the adolescent female. Ann N Y Acad Sci 2000;900:403-8.
9. Jee WS. The interactions of muscles and skeletal tissue. In Lyritis GP (ed) Musculoskeletal Interactions Vol II Hylonome Editions, Athens 1999;35-46.
10. Frost HM. Perspectives: a proposed general model for the mechanostat (suggestion from a new paradigm). Anat Rec 1996;244(2):139-47.
11. Jee WS. H.M Frost's legacy: The Utah paradigm of skeletal physiology. Te Niigata Journal of Health and Welfare 2005; 6: 1-9.
12. Burr DB. Muscle strength, body mass and age related bone loss. J Bone Miner Res 1997;12:1547-1551.
13. Schoenau E, Frost HM. The 'muscle-bone unit' in children and adolescents. Calcif Tissue Int 2002;70(5):405-7.
14. Doyle F, Brown T, Lachance C. Relation between bone mass and muscle weight. Lancet 1970;1(7643):391-3.
15. Jee WS, Tian XY. The benefit of non-mechanical agents with mechanical loading: a perspective based on the Utah Paradigm of Skeletal Physiology. J Musculoskelet Neuronal Interact 2005;5(2):110-8.
16. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis. The critical need for a uniform nomenclature based on their actions on bone remodeling. J Bone Miner Res 2005;20(2):177-84.
17. Meakin LB, Todd H, Delisser PJ,Galea GI, Moustafa A, Lanyon LE, Windahi SH, Price PC Parathyroid hormone's enhancement of bones: osteogenic response to loading is affected by ageing in a dose and time-depended manner. Bone 2017;98:59-67.