J Musculoskel Neuron Interact 2002; 2(3):209-211

Hylonome

Perspective Article

Size, structure and gender: Lessons about fracture risk

R.B. Martin

Orthopaedic Research Laboratories, UC Davis Medical Center, Sacramento, CA, USA

Abstract

The differences in age-related fracture risks among men and women must reflect gender differences in the relevant variables. We are concerned here with gender differences in structural variables that relate to the size and shape of bones. As children grow, their bones grow in diameter through periosteal modeling. Studies show that radial growth is driven by mechanical forces and is not just "genetically programmed". Moving bone mass farther from the center of the diaphysis makes it more effective in resisting bending and twisting forces, and disproportionately so in comparison to changes in bone mass. Gender differences in long bone structure appear to arise because the bone cells of males and females function in different hormonal environments which affect their responses to mechanical loading. In girls, bone formation on the metacarpal periosteal surface essentially stops at puberty, and is replaced by formation on the endosteal surface, reducing endosteal diameter until about age 20. Bone strength is 60% greater in male metacarpals than in those of females because bone is added periosteally in boys and endosteally in girls. At menopause endosteal resorption resumes, accompanied by slow periosteal apposition, weakening cortical structure. Similar phenomena occur in such critical regions as the femoral neck. Another fundamental gender difference in skeletal development is that whole body bone mineral content increases in linear proportion to lean body mass throughout skeletal maturation in boys, but in girls there is a distinct increase in the slope of this relationship at puberty, when estrogen rises. Frost's hypothesis is that this reflects an effect of estrogen on bone's mechanostat set point, and this is increasingly supported by data showing that estrogen and mechanical strain act through a common pathway in osteoblast-like cells. If Frost's hypothesis is correct, the mechanostat is set for maximal effect of mechanical loading on bone gain during the 2-3 years preceding menarche. During the childbearing years, the set point is at an intermediate level, and at menopause, it shifts again to place the skeleton into the metabolic equivalent of a disuse state. The most direct approach to resolving this problem would be to simulate the putative effect of estrogen on the set point itself.

Keywords: Estrogen, Testosterone, Puberty, Modeling, Exercise

The differences in age-related fracture risks among men and women must reflect gender differences in the relevant variables. These variables concern either the mechanical properties of various bones or other components of fracture risk, such as falls. We are concerned here with gender differences in the former, where a distinction can be made between *structural* variables that relate to the size and shape of bones, and those that characterize the properties of the *material* inside. Gender differences in structural variables appear to be much more significant than differences in the material properties of bone tissue[1]. How the structural differences are related to fracture risks is relatively clear, but the sex-based physiologic differences that cause these structural distinctions are less apparent. These are the focus of this perspective.

Long bone diaphyses are subjected to bending and twisting as well as compressive loads. While resistance to compressive loads depends simply on cross-sectional area, resistance to bending and twisting depends on how that area is distributed in the cross-section. Specifically, it depends on the section modulus, i.e., the ratio of the bone's cross-sectional moment of inertia to its outer diameter. (For a brief introduction to engineering mechanics as it applies to the skeleton, see Turner and Burr[2]). This ratio is proportional to the cube of the bone's radius or diameter. As children grow, gain weight, and become more active, the loads on their skeletons increase, and their bones grow in diameter through periosteal modeling. Simultaneously, their hematopoietic capacity must increase, so the diameter of the medullary canal increases through endosteal resorptive modeling. Moving the bone mass farther from the center of the diaphysis makes it more effective in

Corresponding author: R. Bruce Martin, Orthopaedic Research Laboratories, Research Building I, UC Davis Medical Center, 4635 Second Ave., Sacramento, CA 95817, USA. E-mail: rbmartin@ucdavis.edu

Accepted 15 July 2001

resisting bending and twisting forces, and disproportionately so in comparison to changes in bone mass.

Studies of the effects of mechanical loading on growing children's bones[3] show that radial growth is driven by mechanical forces and is not just "genetically programmed". Presumably two things would lead to exceptionally high bone mass at the end of growth: activities which increase skeletal loading, stimulating bone formation, or bone cells that produce more bone for a given amount of loading. In this scenario, gender differences could arise because of cultural factors leading one sex to pursue activities which place greater loads on their bones, and/or because the bone cells of males and females function in different hormonal environments which affect their responses to mechanical loading. The latter appears to be more significant.

Age changes in the endosteal and periosteal diameters of the second metacarpal bone reflect the effect of puberty on cortical bone modeling[4,5]. In girls, bone formation essentially stops on the periosteal surface at puberty, and is replaced by formation on the endosteal surface, continuing until about age 20. Thereafter, there is little change in cortical area until menopause, when endosteal resorption resumes, accompanied by slow periosteal apposition. Boys, on the other hand, continue to add bone to the periosteal surface until near the end of their growth. Between ages 20 and 50 the gender difference in cortical width is small. However, bone strength is 60% greater in the male metacarpals because bone is added periosteally in boys and endosteally in girls.

Animal studies confirm a distinct difference in the effects of the principal sex hormones on skeletal modeling. Periosteal bone formation is arrested when prepubescent female rats are given estrogen[6-8]. On the endosteal surface, estrogen stops resorption but does not provoke formation in this model, as distinct from humans. Conversely, both the periosteal and endosteal diameters of the tibia increase following ovariectomy. In males, periosteal bone formation is reduced following orchiectomy. In cancellous bone of the tibial metaphysis, on the other hand, both ovariectomy and orchiectomy activate remodeling and decrease bone mass. Thus, the primary gonadal hormones of males and females appear to have different effects on cortical bone modeling, but similar effects on trabecular bone volume.

The rat results are consistent with the human bone changes occurring at menarche except for the endosteal surface, where estrogen activates formation in humans (in the metacarpal, at least) but only stops resorption in the rat tibia. Unlike humans, rats do not experience blood loss during their reproductive cycle. Considering the increased demand for hematopoiesis which the onset of the menstrual cycle requires, and the close connections between bone and marrow cells in space and lineage, it is puzzling that marrow is apparently sacrificed to allow increased bone formation when estrogen levels rise in girls. On the other hand, the mechanical effect of losing this inner bone would theoretically be more tolerable than an equivalent loss from the periosteal surface.

There is another gender difference in the way that bone is added at puberty. Whole body bone mineral content (BMC) increases in linear proportion to lean body mass (LBM) throughout skeletal maturation in boys, consistent with the observation that most bone loading is due to muscle forces, which are proportional to LBM[9]. However, the corresponding plot for girls shows a distinct increase in slope near the onset of puberty, when estrogen levels rise. Frost[10] suggested that estrogen lowers the "set point" of the skeleton's putative "mechanostat" control system for strain, increasing the bone mass associated with normal loading. The slope of the BMC/LBM curve can be interpreted as inversely proportional to the mechanostat set point, and the change in slope at the onset of puberty in girls implies an effect of estrogen on this control parameter. Data on circulating estradiol levels in young girls can be used to approximate an estrogen-mechanostat set point dose-response curve based on the changing slope of the Scheissl plot, and these data are consistent with other experimental results[11].

This hypothesis is supported by data showing that mechanical loading and estrogen act synergistically on collagen synthesis in cultured rat ulnas[12], and more recent data indicating that estrogen and mechanical strain act through a common pathway in osteoblast-like cells[13]. When estrogen was present, less mechanical stimulus was required for a given response. If this fundamental property is present in functional osteocytes and osteoblasts, a mechanism for estrogenic control of the mechanostat set point is at hand.

Several studies have examined the effect of increased mechanical loading on bone mass in boys and girls prior to, during, and after puberty[3,11,14]. In interpreting these studies and the data of Schiessl et al., it is important to understand that estrogen levels start to rise in girls at about age 10 and peak at menarche, at which point they rapidly diminish. Consequently, if Frost's hypothesis is correct, the mechanostat is set for maximal effect of mechanical loading on bone gain during the 2-3 years preceding menarche. During the child-bearing years, the set point is at an intermediate level, and at menopause, it shifts again to place the skeleton into the metabolic equivalent of a disuse state. While drugs that block osteoclastic action and/or remodeling may serve to reduce this effect, a more direct approach would be to address the putative effect of estrogen on the set point itself.

References

1. Martin RB. Aging and strength of bone as a structural material. Calcif Tissue Int 1993; 53:S34-S40.
2. Turner CH, Burr DB. Basic biomechanical measurements of bone: a tutorial. Bone 1993; 14:595-608.
3. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, Oja P, Vuori I. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. An Intern Med 1995; 123:27-31.
4. Garn SM. The earlier gain and the later loss of cortical

bone. Charles C. Thomas, Springfield, IL; 1970.
5. Turner CH. Editorial: Do estrogens increase bone formation? Bone 1991; 12:305-306.
6. Turner RT, Hannon KS, Demers LM, Buchanan J, Bell NH. Differential effects of gonadal function on bone histomorphometry in male and female rats. J Bone Miner Res 1989; 4:557-563.
7. Turner RT, Colvard DS, Spelsberg TC. Estrogen inhibition of periosteal bone formation in rat long bones: down-regulation of gene expression for bone matrix proteins. Endocrinology 1990; 127:1346-1351.
8. Turner RT, Wakley GK, Hannon KS. Differential effects of androgens on cortical bone histomorphometry in gonadectomized male and female rats. J Orthop Res 1990; 8:612-617.
9. Schiessl H, Frost HM, Jee WSS. Estrogen and bone-muscle strength and mass relationships. Bone 1998; 22:1-6.
10. Frost HM. Bone "mass" and the "mechanostat": a proposal. Anat Rec 1987; 219:1-9.
11. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD. Prospective ten-month exercise intervention in pre-menarchal girls: positive effects on bone and lean mass. J Bone Miner Res 1997; 12:1453-1462.
12. Cheng MZ, Zaman G, Rawlinson SC, Suswillo RF, Lanyon LE. Mechanical loading and sex hormone interactions in organ cultures of rat ulna. J Bone Miner Res 1996; 11:502-511.
13. Zaman G, Cheng MZ, Jessop HL, White R, Lanyon LE. Mechanical strain activates estrogen response elements in bone cells. Bone 2000; 27:233-239.
14. Heinonen A, Sievanen, Kannus P, Oja P, Pasanen M, Vuori I. High-impact exercise and bones of growing girls: a 9-month controlled trial. Osteoporos Int 2000; 11:1010-1017.