PERSPECTIVE

Estrogen and Bone-Muscle Strength and Mass Relationships

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The **largest voluntary** loads on **bones come** from muscles: To **adapt bone strength and mass to them, special strain threshold** ranges determine where modeling adds and strengthens bone, and where remodeling conserves or removes it, just as different thermostat settings control the heating and cooling **systems in a house- If estrogen lowers the remodeling threshold, two things should occur. First, at** puberty in girls, bone mass should begin to increase more than in boys with similar **muscle strengths, owing to reduced remodeling-dependent bone losses, while gains from longitudinal** bone growth and **bone** modeling continue normally. **That increase in** bone **mass** in girls should plateau when **their muscle strength** stops **increasing, since their stronger bones** could then reduce bone **strains enough to turn modeling off, but** could let remodeling **keep conserving existing bone. 'Second, decreased estrogen secretion [or a related factor(s)], as during menopause, should raise the remodeling threshold and make remodeling begin removing that extra bone. That removal should also tend to plateau after the remaining and weaker bone lets bone strains** rise to the higher threshold. Postmenopausal bone loss **shows the second effects. Previously unremarked relationships in the data of a 1995 Argentine study showed the first effects. This supports the idea that estrogen** can **affect human** bone strength and mass by lowering the remodeling threshold, and loss of estrogen would raise the threshold and help cause postmenopausal bone loss even if other factors help to do it. **The** Argentine study also suggested ways to study those things and the roles of muscle strength and other factors **in controlling** bone strength and mass in children and adult humans_ Those factors include, in part, **hormones, vitamins, calcium, diet, sex, race, age,** medications, cytokints, **genetic errors, gene expression** patterns, and disease, (Bone 22:1-6; 1998) © 1998 by Elsevier Science **Inc. All rights reserved.**

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> Between muscle and bone there can be no change in the one but it is correlated with changes in the other ." (D'Arcy Thompson, 1917)

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Introduction

In most women, accelerated loss of bone next to marrow (spongiosa and endocortical bone) begins at menopause and continues until **75%-85%** of the premenopausal bone mass remains. Then further losses usually fall to and plateau at age-normal lower rates ("mass" has its meaning in absorptiometry here).[39] Efforts to explain that took two main tracks.

Biochemical and **cell-biologic explanations** focused on osteoclasts and/or osteoblasts and their responses to things such as parathyroid hormone, calcium, and estrogen One idea suggested that loss of osteoclast depression by estrogen causes postmenopausal bone loss.[1,33] Another idea **suggested that loss of** an estrogen effect on osteoblasts reduces their activity relative to osteoclastic activity to increase bone losses and cause osteopenta (less bone than normal).[20,31,36,40] If so. and other things being equal, the hormone could help keep an existing bone mass. but would not increase- it: Decreased hormone secretion should increase bone losses on all bone envelopes (periosteal. Haversian. endocortical, and trabecular surfaces), and as long as the decreased secretion continued the losses should not fall to and plateau at lower rates.[12]

A newer explanation depends on bone-modeling drifts, remodeling basic multicellular units (BMUs). their thresholds. and their responses to mechanical influences. It suggests that estrogen [or a related factor(s)] could lower the bone strain threshold that helps remodeling to control conservation and removal of bone.[4,9,14,28] If so, and other things staying equal. (1) Increased estrogen secretion at puberty should make girls add more bone than before **in relation to the mechanical** loads on their bones. but later. that gain should tend to plateau even though estrogen **secretion continues.** (2) Decreased hormonal levels during menopause **would Increase bone loss. which later on should** tend to plateau. too, even though estrogen levels remained low

Postmenopausal bone loss clearly reveals the latter effects Relationships **noted in data** from an Argentine study reveal the former **effects, too**[47] **Summarized below. that study also suggested safe and** noninvasive ways to study how varied factors affect rhe rnodeling and remodelin, thresholds and their effects on bone strength and mass in p-owing **and adult humans** Explaining how the Argentine data support the newer- **explanation depends** on some **physiology.** Summari zed **next**

Pertinent Bone Physiology

Neoplasms, **infection. and** longitudinal bone growth excepted global bone modeling by drifts provides the chief mechanism for Increasing our bone strength and mass, while global BMU-based **remodeling provides the chief mechanism for removing mechanically unneeded bone** [4,10,11,15,22,25,32] **No** evidence known to us

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shows that modeling reduces bone strength and mass or that remodeling increases them (“global” means averaged over whole bones or skeletons).

Where bone strains frequently exceed a modeling threshold range that may center near 1000 microstrain, modeling begins to increase bone strength and mass. Where strains stay below that threshold, mechanically controlled modeling stops increasing bone strength and mass.[5,10,12,15,23–30,45] For comparison, bone fractures at ≈25000 microstrain.[32] Modeling becomes relatively ineffective in cortical bone in adults, but it can apparently affect trabeculae throughout life.

Where bone strains stay in or below a lower remodeling threshold range, as in disuse, BMU creations increase on all bone envelopes, while in bone next to marrow completed BMUs make less bone than before. Yet, BMUs keep resorbing and making nearly equal amounts of bone on the Haversian envelope, since permanent Haversian porosity does not increase, excepting a quite small age-related increase, and transient remodeling space effects.[32,38] This “disuse-mode” remodeling begins to cause permanent losses of bone only where it touches marrow. This reduces bone strength and mass and can cause osteopenia. Where strains exceed this threshold, resorption and formation in completed BMUs next to marrow begin to equalize. This conservation mode of remodeling begins to conserve existing bone mass, which tends to prevent osteopenia or progression of an existing one.[11,17] This little-studied remodeling threshold range may center near 50–100 microstrain.

The difference between the amount of bone resorbed and made by the typical completed BMU has been signified by p.[7] When that resorption and formation are equal, p = 0 (i.e., no difference in their amounts), as on the Haversian envelope and in conservation-mode remodeling. When BMUs make less bone than they resorb, p is negative (less formation than resorption), as in bone next to marrow and in disuse-mode remodeling. It seems BMU creations and p need not always respond in the same sense to some agents. For example, when bone microdamage increases, BMU creations can increase on all bone envelopes to repair it,[34] and p tends toward zero on those envelopes. Yet, during acute disuse, BMU creations can increase on all envelopes and p still tends toward zero on the Haversian *envelope*, but it goes markedly negative where bone touches marrow.[12] This should explain why the resulting bone loss comes from bone next to marrow. In effect, p would determine if and where remodeling conserves or removes bone, while BMU creations would affect only the rates of remodeling-dependent bone turnover and net losses.

The modeling and remodeling thresholds can determine where bone strength and mass do or do not satisfy the mechanical demands on them, and where existing bone is or is not needed for mechanical reasons. In principle, many factors could change the set points of those thresholds. The end of the Abstract listed some examples. This article concerns possible effects of estrogen [or a related factor(s)] on the remodeling threshold.

Those arrangements normally make modeling and remodeling adapt a bone’s strength and mass to the largest strains caused by voluntary physical activities[10,11]. Trauma excepted, muscles cause the largest strains, since muscle forces on bones must overcome two resistances to move us around during work and play. Body weight provides the first resistance. The poor lever arms most muscles work against provide the second and larger resistance.[6,32,35,43] As a result, it takes more than 2 kg of muscle force on bones to move each kilogram of body weight around on earth.[6,32,43]

This means whole-bone strength should correlate better with muscle strength than with age or body weight alone, an old idea[44] that recent studies support.[41,42] Bone modeling and remodeling have other functions and determinants that are not discussed here.

In children, bone strength and mass increase chiefly because longitudinal bone growth and modeling add bone faster than remodeling removes it.[2] In adults, modeling nearly ceases but remodeling does not, which helps to cause a slow, age-related expansion of marrow cavities, thinning of bone cortices, and net losses of spongiosa. It should follow that if conservation-mode remodeling became more efficient during growth, continued longitudinal bone growth and bone modeling would increase bone mass more rapidly than before.

Bone’s materials properties change little with age, species, and sex,[8,18,32] so increased bone strength usually accompanies increased bone mass, too. In healthy subjects, that means bone mass can provide useful indices of whole-bone strength as well as of the amount of bone tissue in whole bones.[8,18,32]

Predictions

If estrogen [or a related factor(s)] lowers the remodeling threshold, the above physiology would predict five effects. (1) In girls near puberty, bone strength and mass should begin increasing faster than before, since the previous remodeling-dependent bone losses would decrease while modeling-dependent additions of bone would continue normally. (2) At the same time, bone mass should begin increasing faster than in boys with similar muscle strengths (not with similar body weights or ages). (3) In girls, that increase in bone mass should plateau when muscle strength stops increasing, even though estrogen secretion continues, because then their strengthened bones could reduce strains to the modeling threshold and turn modeling off, but still leave conservation-mode remodeling on. (4) Reduced estrogen secretion at some later time should raise the remodeling threshold and make disuse-mode remodeling remove that extra bone and cause osteopenia. (5) That loss should also tend to plateau after the remaining weaker bone lets strains rise to the higher remodeling threshold and turns conservation-mode remodeling back on, even though reduced estrogen secretion continues.[9]

A summary follows of data that could test the previously untested first three of those five predictions.

The 1995 Argentine Study

Zanchetta et al.[47] used dual-energy X-ray absorptiometry (DXA) to estimate, among other things, total body bone mineral content (TBMC) and lean body mass (LBM). In 778 healthy Argentine Caucasian children (345 boys and 443 girls) between 2 and 20 years of age. The children were not selected by economic status. To ensure normal values, the study excluded children with weight or height more than 2 standard deviations different from the norm, as well as children receiving medications known to affect bone physiology and children with a bone age more than 1 year different from the chronological age. The data were tabulated as means of 1-year age groups, so children in any 1-year age group were more than 6 months older than the previous age group and <6 months younger than the next one. The children were studied in random order with respect to age and sex. A Norland XR-26 HS densitometer with dynamic filtration made the measurements after calibration each day against inert phantoms. For the measurements considered below, the repeatability as the coefficient of variation = 1.5%–2.0%.

The TBMC values in Table 1 provide an index of the total amount of bone in the skeleton, and thus of bone strength. The lean body mass values in Table 2 provide an index of the total amount of muscle in the body, and thus of muscle strength. For those girls and boys, Figure 1 plots the grams of bone mass on

Table 1. Whole body bone mineral content (g)

Age	Males n	Males WBMC	Males SD	Females n	Females WBMC	Females SD
2	6	431	47	5	344	89
3	10	494	49	13	446	79
4	16	527	82	15	505	92
5	15	665	77	17	671	30
6	17	724	35	21	717	25
7	25	856	96	22	813	108
8	24	1024	167	33	878	171
9	26	1023	162	37	1049	210
10	37	1186	225	49	1196	284
11	23	1334	219	34	1257	274
12	24	1438	251	29	1533	393
13	28	1779	312	35	1964	430
14	24	2094	340	23	2238	313
15	22	2364	323	31	2228	385
16	17	2625	309	16	2397	288
17	12	2825	309	26	2397	283
18–20	19	2964	345	19	2368	349
	Σ = 345			Σ = 433		

Age is given in years ± 6 months. n = number of subjects in each 1-year age group; Σ = sum of the n's for the whole study; WBMC = whole-body bone mineral content in grams for the 1-year age groups; SD = 1 standard deviation in grams for 1-year age groups. Data were taken from Table 2 in Zanchetta et al.,[47] with values rounded off to two to four significant figures.

the vertical axis that correspond to the grams of lean body mass on the horizontal axis. Each of its data points provides the mean of all boys or girls in the same 1-year age group. It does not compare bone mass to age or whole-body weights.

Figure 1 shows that at 11–12 years of age, the bone mass index began increasing faster in girls than before. It also increased faster than in boys with the same muscle mass indices. By 14–15 years of age, the muscle index plateaued in girls, as shown by the closely grouped data points for their 15–20-year-old groups on the far right of the curve. Their bone mass index also plateaued then, and at a higher level than for boys with the same muscle mass index. Since the muscle and bone indices were still increasing in boys at the study's limit at 20 years of age, most 20-year-old men ended up with more muscle and bone than most 20-year-old women.

Table 2. Lean body mass (g)

Age	Males n	Males LBM	Males SD	Females n	Females LBM	Females SD
2	6	10,510	1200	5	8730	6370
3	10	13,380	720	13	11,530	1490
4	16	13,960	1600	15	12,300	1560
5	15	15,710	1490	17	15,610	3900
6	17	18,140	1470	21	16,210	2050
7	25	20,160	1980	22	17,620	2210
8	24	21,630	2230	33	18,650	2150
9	26	22,920	2570	37	20,930	3110
10	37	25,530	2190	49	21,810	3330
11	23	26,060	3220	34	23,930	3840
12	24	30,490	3950	29	27,510	3410
13	28	35,540	4920	35	28,860	3630
14	24	40,780	5810	23	31,710	3350
15	22	46,960	5340	31	31,620	4530
16	17	49,300	4350	16	30,220	3680
17	12	51,760	5530	26	31,540	3850
18–20	19	53,470	3600	19	31,630	5400
	Σ = 345			Σ = 433		

Age is given in years ± 6 months. n = number of subjects in each 1-year age group; LBM = mean lean body mass in grams for the 1-year age groups; SD = 1 standard deviation in grams for the 1-year age groups; Σ = sum of the n's in the whole study. Data were copied from Table 6 in Zanchetta et al.,[47] but converted from kilograms to grams.

Comments

Summary

This may be the first comparison of human whole-body bone mass to an index of whole-body muscle strength in the above age span; past studies usually compared whole-body bone mass to age or whole-body weights. When interpreted in the context of the physiology summarized earlier, the present comparison reveals some provocative information. While the usual postmenopausal bone loss shows the predicted initial bone loss and later plateau, Figure 1 reveals the estrogen-associated gain in bone mass at puberty, its association with growing lean body mass, the difference in this respect between girls and boys with similar lean body masses, and the later plateaus in bone and muscle mass in girls, all of which were predicted earlier.

Given qualifications in the next subsection, those observations lend support to six things: (1) Each prediction given earlier; (2) the idea that muscle strength has a major influence on postnatal bone strength and mass; (3) the idea that some nonmechanical agents including estrogen can modify the modeling and/or remodeling thresholds to affect bone strength and mass; (4) a classification of osteopenias and osteoporoses that depends on their biomechanical pathogenesis[17]; (5) the paradigm of skeletal physiology from which those ideas come[12,14–16,25,26]; and (6) proposals in the sections below.

Why did comparisons of bone mass to age or whole-body weights fail to reveal the above effects? Consider that lean body mass forms a smaller fraction of whole-body weight in girls than in boys, and the difference increases after puberty. The lean body mass fractions of these Argentine children, of 76% in girls and 80% in boys at 8 years of age, changed to 63% and 79%, respectively, by age 14, and to 57% and 76%, respectively, by 18–20 years of age (calculated from body weights in Table 1 of the Argentine report[47]; data not shown here; and in Table 2 of this article). Accordingly, if muscle strength influences bone strength and mass more than age or body weight, comparing age and/or whole-body weights to bone mass could minimize or conceal the lean body mass influence on bone mass. This may have happened in past comparisons of bone mass to male–female ages and whole-body weights.[39] It did happen in graphs in the Argentine report[47] that compare bone mass to age in the girls and boys.

Further Studies, and With Better Indices?

We realize the above findings would need confirmation by other studies, partly because of methodological and analytical uncertainties in using total bone mineral content and lean body mass as bone and muscle strength indices, and partly owing to the potential importance of those findings, which support ideas some authorities could view as controversial. Besides other sampling strategies and later DXA equipment and software, other indices could help in doing such studies. As examples, muscle strength can be measured easily in humans to eliminate the uncertainties of lean body mass estimates.[7,27,41] In particular bones and with suitable software, peripheral quantitative computed tomography (pQCT) can provide reliable bone strength indices (BSIs) that account for both the mass and architectural contributions to bone

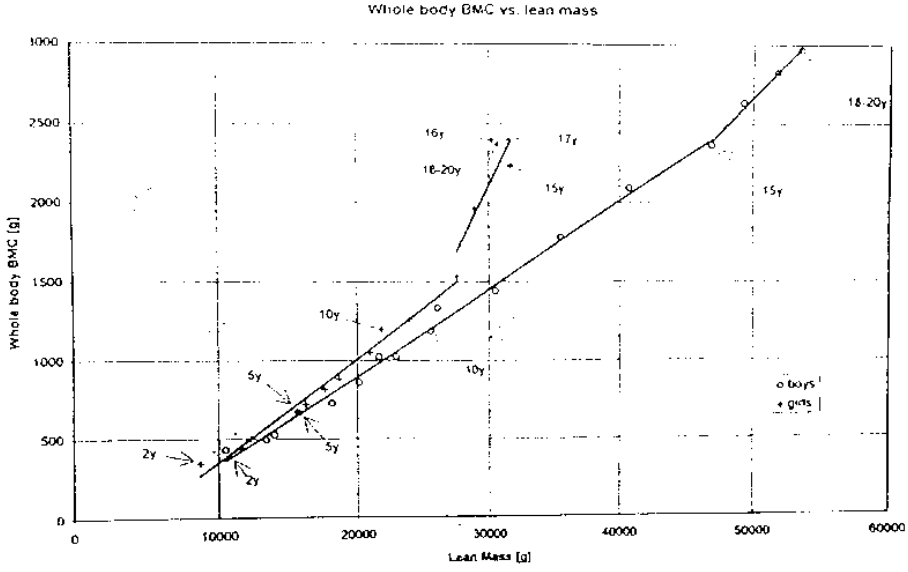

Figure 1. From data in Tables 1 and 2, this figure plots the grams of bone mineral content (TBMC) on the vertical axis that correspond to the grams of lean body mass (LBM) on the horizontal axis. Crosses: girls; open circles: boys. The text assumes the TBMC provides an approximate but useful index of bone strength, and the LBM provides an approximate but useful index of muscle strength. Going from left to right, each data point on each curve stands for an age 1 year older than the data point to its left, and it shows the mean bone and muscle indices for all subjects in that 1-year age group ("n" in the tables). This figure's two curves plot the findings in 345 boys and 443 girls. For similar lean body masses (the muscle index), around 11–12 years of age bone mass begins to increase faster in girls than in boys. By 14–15 years of age, bone and lean body mass both plateaued in girls, as shown by the closely grouped data points for their 15–20-year age groups on the far right side of their curve. Yet, both indices were still increasing in the 20-year-old males. In the figure and tables, the 18–20-year age groups combine as a single data point for girls, and another for boys. The data points for girls aged 14 and 15 years overlap.

strength.[8,19,41,42] Ferretti[8] found that they correlated better with fracture strength in long bones ($r > 0.94$, $p < 0.0001$) than bone mineral content alone ($r \approx 0.7$, $p < 0.0001$).

What Problems Might Studies Such as the One Illustrated in Figure 1 Address?

Besides questions about methodology, such studies could help to evaluate physiologic questions that are not easily studied by other means in humans. A few such questions follow.

Would ovariectomy, orchiectomy, and other hypogonadal situations affect the above thresholds and bone–muscle relationships? And other hormones? And some diseases? And different sports, diets, calcium intakes, vitamins, and cytokines? Do they differ in some osteoporoses, as suggested recently?[17] Do they differ in blacks or other races? Do some medications affect them? Do they exist in mice, rats, dogs, sheep, and primates? Do the modeling and remodeling thresholds not change at puberty in boys? Which skeletal compartment(s) stores the extra bone in girls (see the next subsection)? Would supplemental estrogen have similar bone effects in growing and/or adult males? Does the increased horizontal spacing between the data points for boys between 10 and 15 years of age partly reflect an androgen-induced acceleration of growing muscle strength after male puberty, an acceleration that increases bone mass, too?[2] What happens to these relationships after 20 years of age? Does estrogen affect muscle strength?

Some Speculation About Estrogen Effects on the Modeling and Remodeling Thresholds

The following ideas are offered simply for discussion, following invitations to do so. Any blame for these "trial balloons" should be directed at the second author (HMF). First we offer some observations, then some assumptions to explain them.

Observations. (1) At menopause, BMU creations increase on all bone envelopes. When women going through menopause take estrogen, BMU creations decrease on all envelopes. (2) When estrogen deficiency begins, ρ tends toward zero on the Haversian envelope, but next to marrow it goes very negative. This increases bone loss, but only next to marrow. Restoring estrogen changes ρ back toward zero next to marrow, which minimizes further losses of that bone.[20,37] (3) For biomechanical reasons, lowering the modeling threshold should increase periosteal formation drifts, which should increase the outside diameters of long bones. So far, we know of no evidence that estrogen has this effect.

The assumptions. (1) Estrogen lowers the remodeling threshold for BMU creations on all envelopes. (2) Separately, it affects something in marrow that secondarily makes loss of estrogen make ρ go more negative in BMUs next to marrow (as an aside, estrogen increases bone formation in the marrow cavity in birds and mice, and only there). (3) Estrogen does not affect the modeling threshold, contrary to the former idea that it might.[9]

Right or wrong, those assumptions could explain the above observations, as well as the evidence in Figure 1. If girls at menarche do store extra bone next to marrow instead of—or as well as?—on periosteal surfaces, DXA or pQCT studies should show it.

A Possible Reason for Estrogen's Bone Effects?

Could estrogen make growing females add more bone than their physical activities need, to store extra calcium for later lacta-

tion.[45] By the time of birth, a mother's placental circulation supplies a relatively small amount of calcium to the fetal skeleton, but her milk must provide many times that amount between birth and weaning to let her infant's rapidly growing bones mineralize properly.[46] Given the calcium content of most diets in premodern times, the calcium provided during lactation should come from both her diet and her bone.

If so, when menopause makes pregnancy impossible, that extra bone would become unnecessary. Reduced estrogen secretion would raise the remodeling threshold and make disuse-mode remodeling begin removing the extra bone. That removal should cease when strains of the remaining weaker bone increased enough to make conservation-mode remodeling begin conserving it.

That explanation views postmenopausal bone loss per se as physiology, not a disease. In support of it, bones exist mainly to carry voluntary loads without breaking spontaneously or causing pain, and few postmenopausal women have such problems. Instead, falls due to impaired balance usually cause any fractures they have.[17,19] Of course, their postmenopausal osteopenia does make falls more likely than before to cause fractures, usually of extremity bones.

Conclusion

Eight decades after D'Arcy Thompson penned the words that opened this article, we just begin to perceive their merit and implications and the biologic mechanisms, processes, and relationships that make them true.

Acknowledgments: The bone and muscle mass relationships recorded in tables in the article by Zanchetta et al.[47] were perceived by Hans Schiessl, who brought them to the attention of Dr. Frost and Dr. Jee. Those relationships seemed important enough to justify writing an article to describe and discuss them, so Dr. Frost and Dr. Jee wrote this one. However, they both believe Hr. Schiessl deserves the credit for perceiving those relationships, which otherwise could have gone unnoticed for years. Doctor Frost and Dr. Jee had not perceived them, but could help to explain them. Accordingly, they list him as first author of this article, and themselves as second and third authors.

References

1. Barzel, U. S. Osteoporosis. New York: Grune and Stratton; 1970.
2. Bhasin, S., Storer, T. W., Berman, N., Callegari, C., Clevenger, B., Phillips, J., Bunnell, T. J., Tricker, R., Shirazi, A., and Casaburi, R. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7; 1996.
3. Buckwalter, J. A., Woo, S. L.-Y., Goldberg, V. M., Hadley, E. C., Booth, F., Oregema, T. R., and Eyre, D. R. Soft tissue aging and musculoskeletal function. J Bone Jt Surg 75A:1533–1548; 1993.
4. Burr, D. B. and Martin, R. B. Errors in bone remodeling: Toward a unified theory of metabolic bone disease. Am J Anat 186:1–31; 1989.
5. Burr, D. B. and Martin, R. B. Mechanisms of bone adaptation to the mechanical environment. Triangle 31:59–76; 1992.
6. Crowninshield, R. D., Johnston, R. C., Andrews, J. G., and Brand, R. A. A biomechanical investigation of the human hip. J Biomech 11:75–85; 1987.
7. Faulkner, J. A., Brooks, S. V., and Zerva, E. Skeletal muscle weakness and fatigue in old age: Underlying mechanisms. In: Cristofalo, V. J. and Lawton, M. P., Eds. Annual Review of Gerontology and Geriatrics. New York: Springer-Verlag; 1990. 147–166.
8. Ferretti, J. L. Perspectives of pQCT technology associated to biomechanical studies in skeletal research employing rat models. Bone 17(Suppl):353–364; 1995.
9. Frost, H. M. The mechanostat: A proposed pathogenetic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 2:73–85; 1987.
10. Frost, H. M. Structural adaptations to mechanical usage (SATMU). 1. Redefining Wolff's Law: The bone modeling problem. Anat Rec 226:403–413; 1990.
11. Frost, H. M. Structural adaptations to mechanical usage (SATMU). 2. Redefining Wolff's law: The bone remodeling problem. Anat Rec 226:414–422; 1990.
12. Frost, H. M. Introduction to a New Skeletal Physiology. Vols. I and II. Pueblo, CO: Pajaro Group; 1995.
13. Frost, H. M. A proposal about the roles of estrogen effects on bone suggested in a text distributed to 50 colleagues in the USA and overseas in 1995. Unpublished.
14. Frost, H. M. Perspectives: A proposed general model of the mechanostat (suggestions from a new paradigm). Anat Rec 244:139–147; 1996.
15. Frost, H. M. Bone development during childhood: Insights from a new paradigm. In: Schönau, E., Ed. Paediatric Osteology. New Trends and Developments in Diagnostics and Therapy. Amsterdam: Elsevier Science; 1996; 3–39.
16. Frost, H. M. Perspectives: Why do long distance runners not have more bone? A vital biomechanical explanation and an estrogen effect. J Bone Miner Metab 15:9–16; 1997.
17. Frost, H. M. Defining osteopenias and osteoporoses: Another view (with insights from a new paradigm). Bone 20:385–391; 1997.
18. Gasser, J. A. Assessing bone quantity by pQCT. Bone 17(Suppl):145–154; 1995.
19. Greenspan, S. L., Myers, E. R., Maitland, L. A., Resnick, N. M., and Hayes, W. C. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. JAMA 271:128–133; 1994.
20. Han, Z.-H., Palnitkar, S., Rao, D. S., Nelson, D., and Parfitt, A. M. Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: Implications for mechanisms of bone loss. J Bone Miner Res 12:498–508; 1997.
21. Henderson, K. N., Price, R. I., Cole, J. H., Gutteridge, D. H., and Bhgat, C. I. Bone density in young women is associated with body weight and muscle strength but not dietary intakes. J Bone Miner Res 10:384–392; 1995.
22. Jee, W. S. S. The skeletal tissues. In: Weiss, L., Ed. Cell and tissue biology: A textbook of histology. Baltimore: Urban and Schwartzenberg; 1989; 211–259.
23. Jee, W. S. S. and Li, X. J. Adaptation of cancellous bone to overloading in the adult rat: A single photon absorptiometry and histomorphometry study. Anat Rec 227:418–426; 1990.
24. Jee, W. S. S., Li, X. J., and Schaffler, M. B. Adaptation of diaphyseal structure with aging and increased mechanical usage in the adult rat: A histomorphometrical and biomechanical study. Anat Rec 230:332–338; 1991.
25. Jee, W. S. S. and Frost, H. M. Skeletal adaptations during growth. Triangle 31:77–88; 1992.
26. Kannus, P., Sievanen, H., and Vuori, L. Physical loading, exercise and bone. Bone 18(Suppl 1):1–3; 1996.
27. Kritz-Silverstein, M. and Barrett-Connor, E. Grip strength and bone mineral density in older women. J Bone Miner Res 9:45–51; 1994.
28. Lanyon, L. E. Using functional loading to influence bone mass and architecture. Objectives, mechanisms, and relationship with estrogen of the mechanically adaptive process in bone. Bone 18(Suppl 1):37–43; 1996.
29. Li, X. J. and Jee, W. S. S. Adaptation of diaphyseal structure to aging and decreased mechanical loading in the adult rat: A densitometric and histomorphometric study. Anat Rec 229:291–297; 1991.
30. Li, X. J., Jee, W. S. S., Chow, S. Y., and Woodbury, D. M. Adaptation of cancellous bone to aging and immobilization in the rat: A single photon absorptiometry and histomorphometry study. Anat Rec 227:12–24; 1990.
31. Lindsay, R. and Tohme, J. F. Estrogen treatment of patients with established postmenopausal osteoporosis. Obstet Gynecol 76:290–295; 1990.
32. Martin, R. B. and Burr, D. B. Structure, Function and Adaptation of Compact Bone. New York: Raven; 1989.
33. McLean, F. C. and Urist, M. R. Bone, 2nd ed. Chicago: University of Chicago Press; 1961.
34. Mori, S. and Burr, D. B. Increased intracortical remodeling following fatigue damage. Bone 14:103–109; 1993.
35. Nordin, M. and Frankel, V. H. Basic biomechanics of the musculoskeletal system. 2nd ed. Philadelphia: Lea and Febiger; 1989.
36. Oursler, M. J., Landers, J. P., Riggs, B. L., and Spelsberg, T. C. Oestrogen effects on osteoblasts and osteoclasts. Ann Med 25:361–371; 1993.
37. Parfitt, A. M. Skeletal heterogeneity and the purposes of bone remodeling. In: Osteoporoses. New York: Academic; 1996; 315–329.
38. Recker, R. R. Bone histomorphometry: Techniques and Interpretation. Boca Raton, FL: CRC; 1983.

39 Riggs, B. L. and Melton, L. J., III. Osteoporosis Etiology, Diagnosis and Treatment. 2nd ed. Hagerstown, MD: Lippincott-Raven, 1995.

40 Rodan, G. A., Raisz, L. G., and Bilezikian, J. P. Pathophysiology of osteoporosis. In: Bilezikian, J. P., Raisz, L. G., and Rodan, G. A., Eds. Principles of Bone Biology. Boston: Academic, 1996; 979–990.

41 Schiessl, H., Ferretti, J. L., Tysarczyk-Niemeyer, G., and Willnecker, J. Noninvasive bone strength index as analyzed by peripheral quantitative computed tomography (pQCT). In: Schonau, E., Ed. Paediatric Osteology. New Developments in Diagnostics and Therapy. Amsterdam: Elsevier, 1996; 141–146.

42 Schönau, E., Werhahn, E., Schiedermaier, U., Mokov, E., Scheidhauer, K., Rietschel, E., Haverkamp, F., Schiessl, H., and Michalk, D. Bone and muscle development during childhood in health and disease. In: Schonau, E., Ed. Paediatric Osteology. New Developments in Diagnostics and Therapy. Amsterdam: Elsevier; 1996; 147–160.

43 Simon, S. R., Radin, E. L. Biomechanics of joints. In: Kelly, W. N., K., Harris, E. D., Ruddy, S., and Sledge, C. B., Eds. Textbook of Rheumatology. Philadelphia: WB Saunders, 1993; 1675–1678.

44 Thompson, D. W. On Growth and Form. London: Cambridge University Press, 1917.

45 Turner, C. H. and Forwood, M. R. Bone adaptation to mechanical forces in the rat tibia. In: Odgaard, A. and Weinans, H., Eds. Bone Structure and Remodelling. London: World Scientific, 1995; 65–78.

46 Vaughn, V. C., McKay, R. J., and Nelson, W. E. Nelson Textbook of Pediatrics. 10th ed. Philadelphia: WB Saunders, 1975.

47 Zanchetta, J. R., Plotkin, H., and Alvarez-Figuetra, M. L. Bone mass in children: Normative values for the 2–20-year-old population. Bone 16(Suppl): 393–399, 1995.

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