The Influence of Activity on Calcium Metabolism

G. Donald WHEDON

Medical Research Programs, Shriners' Hospitals for Crippled Children, International Shrine Headquarters, Tampa, Florida, U.S.A.

The term "activity" in the title is intended to include all degrees, from vigorous exercise down to inactivity as extreme as immobilization. It is easier to start this review with effects at the low end of the scale rather than the high, because there have been many more studies, and in greater detail with inactivity than with exercise. This presentation is a modification and an up-date of an earlier review (1).

Effects of inactivity

While the first study of inactivity was in 1929, when the distinguished nutritionist, David Cuthbertson (2), put some medical students to bed for 7 days, the first detailed study with particular interest in calcium metabolism was during the 1940s by Deitrick et al. (3). Metabolic balance studies showed hypercalciuria and negative calcium balance in four healthy subjects, immobilized in bed for 6-7 weeks. More recently, much longer studies of bed rest in normal subjects have been conducted (4) and calcium loss was found to continue for the many months of bed rest, not subsiding until the subjects were put back on their feet. In these latter studies, loss of bone mass was demonstrated by photon absorptiometry scans of the os calcis; on re-ambulation the density of the heel bone was restored toward normal. In paralytic poliomyelitis (5) the pattern was similar but the degree greater, and loss of calcium continued to the point of bone loss, visible by an ordinary roentgenogram.

Similar losses of calcium from the skeleton were observed in metabolic studies of the astronauts in the Skylab space flights (6) and significant decreases in os calcis density were observed in the three astronauts, who lost the greatest amounts of calcium in the balance studies (7).

Effects of exercise

With regard to the effects on bones from positive activity or physical exercise, several reports have gradually accumulated over the last few years, which in various ways support the premise that physical activity favors bone formation. Thus far, apparently no one has conducted studies in which subjects or patients are observed and measured first in a state of modest activity, and then the same individuals are observed for the effects of a considerable increase in physical activity; rather, all comparative studies have been group versus group.

The best one to date was a comparison by Aloia (8) of two groups, studied at the same time, of postmenopausal women, mean age 53 years and 5.5 years after cessation of menses; one group engaged in exercise classes for 1 h, three times a week, for 1 year. Total body potassium and bone mineral content of the mid-radius showed no significant changes in either group, whereas total body calcium (TB Ca) decreased 2.4% over the year in the sedentary control group, but increased by 2.6% in the exercise group. The derived calcium balances (change in TB Ca/time in days) were -42 mg/day and +42 mg/day respectively; the significance of this difference was calculated at p<0.001.

A similar comparative study was made by Smith and Reddan (9), notable particularly because the mean age of the participants was 82 years. Light to moderate exercise brought about an increase of 4.2% over 36 months in the bone mineral content (BMC) of the distal one-third of the radius whereas BMC in the control group decreased 2.5% over the same period. As the authors concluded, this result suggests than even in the aged, bone
may respond with accretion to increased physical stress.

More recently, in 1983, Krolner et al. (10) compared the effects of exercise versus control, the exercise group taking 1 h twice a week of vigorous activity for 8 months. The lumbar spine mineral content increased 3.5%, whereas that of the control group decreased by 2.7%. In the distal radius, a non-weight-bearing bone, for the exercise group there was an insignificant decrease in mineral content, while for the control group there was a decrease of 3.7%.

Three static group comparisons (by single measurements)—cross country runners versus age-matched non-runners (11), both male and female athletes versus controls at several different levels of activity by history (12, 13), and marathon runners versus age-matched non-runners (14)—revealed expected differences in bone “density.” For a fourth static group comparison, Nilsson and Westlin (15) found a graded difference in density among sedentary and exercising non-athletes and ordinary and world-class athletes. When he split the data of the latter among different sports, there was no significant difference.

Interrelationships of bone and muscle

A few investigators and observations have looked into the association of muscle and bone. In 1935, in rats run for 4 miles a day for 120 days, Donaldson (16) observed a 4 to 7% increase in the weight of the leg bones and a corresponding increase in weight of the leg muscles. More recently, also in running rats (though not so far per day, 2,000 m), Saville and Whyte (17) found that, in comparison with non-running rats, bone calcium content in the hind legs increased in association with an increase in muscle mass, the relationship between muscle mass and bone calcium remaining constant in all animals.

In studies of human beings, Doyle et al. (18) noted a significant positive correlation between the ash weight of the third lumbar vertebra and the weight of the left psoas muscle, and proposed that the weight of a muscle reflects the forces it exerts on bones to which it is attached and that muscle weight is an important determinant of bone mass. Cohn et al. (19) measured total body calcium (TB Ca) and total body potassium (TBK), reflective of muscle, and found a fairly constant ratio of TB Ca/TBK in women through all of the decades measured; in men, however, the ratio rose in later years, probably reflecting a greater loss of muscle than bone toward the end of life.

Attempts to reverse bone loss by exercise

Only one investigative group has systematically measured the effects of various efforts to reverse in the same individuals the calcium and bone losses of inactivity. In bed rest research (at the Public Health Service Hospital in San Francisco), sponsored by the National Aeronautics and Space Administration, attempts have been made to develop ways which would protect astronauts’ skeletons in future long duration space flights. The effects have been tested, using static and intermittent compression (by strong, wide spring bands around shoulders to feet), intermittent weight-loading (against the bottoms of the feet), and exercise in bed with and without resistance (20, 21). None of these measure had more than suggestive effects upon either measured calcium metabolic balances or upon density of the os calcis. In an effort to determine how strong an equivalent measure to weight-bearing activity would have to be devised for long-term weightless astronauts, the PHS investigators found that 3 h of quiet standing a day had a partial effect, while it took 4 h a day of ambulation to prevent loss of mineral if the remaining 20 h a day were spent in bed (21).

In an uncontrolled effort to seize the immediate opportunity to try to deal with the problem, astronauts during the last Skylab space flight (SL-4, 86 days) used heel-raising exercises against resistance and a simplistic form of “treadmill,” devised by an associate engineer-astronaut. The decrease in leg muscle mass, measured at the end of the flight, was significantly less than that observed in the two prior Skylab flights (22), but data on urinary calcium, calcium balance and os calcis density gave no indication of any impact on hypercalciuria, or bone loss (23). Particularly from these space flights and related bed rest studies, the conclusion thus far reached, with regard to the kind of exercise or physical activity which acts to preserve, let alone increase, skeletal mass must be mainly gravitational in character, and probably involves the several various physiological factors involved in standing and walking.
Mechanisms by which mechanical loads influence bone structure

Timely to a consideration of mechanisms was a Kroc Foundation conference held in July, 1983, entitled "Functional Adaptation in Bone Tissue" (24). Pertinent sections of the summary of the conference are as follows:

"The main focus of the conference was on the possible mechanisms by which mechanical loads influence bone structure. The starting premise is that the bone's loading regimen influences the behavior of cell populations whose response is either to maintain or to change the shape and internal organization of the bone. Physical forces in some way have to tell bone tissue whether or not to favor bone formation versus bone resorption, and in what specific areas. This capacity for mechanically adaptive remodeling requires:

1) a mechanism for the transduction of the physical signal into a chemical message capable of influencing cell behavior,
2) amplification and appropriate spatial distribution of the message, and
3) responses by effector cells which may be site specific, and which may be modulated by systemic and additional local influences.

"The nature of the physical signal(s) perceived by the cells is not yet known. The immediate consequences of mechanical loading are strains within the calcified matrix which may be transmitted to osteocytes and lining cells directly, and which also cause pressure gradients in the fluid and hence fluid flow and electrical streaming potentials within the various channels and interstices of the bone matrix. Piezoelectric forces from deformation of bone crystals are also a possible source of influence on bone cells. A number of experiments suggest that bones can remodel according to changes in strain distribution, as well as to the strain rate and strain magnitude. Electrical charges of the same order of magnitude as the streaming potentials produced by physiological strain have been shown to influence cellular behavior, so that this mechanism could provide a regulatory pathway independent of, but perhaps supplementary to, that provided by putative chemical mediators.

"Experimental work has shown that cells of the osteoblast lineage respond to prostaglandin release by stretching the substrate on which they grow. Involvement of prostaglandins in signal mediation is an attractive hypothesis for several reasons, but how it may exert site specific efforts is an unsolved problem.

"Regardless of the means by which a mechanically derived signal is generated and what it is (or they are), it is at the level of the responding cell population that the signal interacts with systemic and other local influences. The result of this interaction determines the cell population's response, which may be either to maintain the remodeling status quo, or to alter its course and direction."

Summary

Many studies and observations have shown the bone-losing effects of physical inactivity of various forms. Contrariwise, less precise studies and observations have supported the reasonable premise that mechanical loading of the skeleton via physical activity shifts the balance of bone remodeling in favor of bone formation, and appears to do so at all ages. Some interesting starts have been made in research to discover the mechanisms of the action on bone of mechanical loading, but many pathways remain to be explored. Besides the mechanical forces, we need to know more about the interrelations of muscle function, probably mediated through muscle-tendon pull on periosteum, and more about other likely influences, notably changes in circulation to bones.

The practical significance relative to calcium metabolism and aging of what has been learned thus far on the effects of activity, is that prolonged inactivity, either in a chair or in bed, is to be avoided, because of its deleterious effects, and that reasonably energetic gravitational exercise, such as walking or possibly jogging, promotes maintenance of bone health.

REFERENCES

1) Whedon, G.D. (1982): Interrelation of physical activity and nutrition on bone mass, in Proceedings of A.M.A. Symposium on Diet and Exercise: Synergism in Health Maintenance, November, 1981. ed. by White, P.L., American Medical Association, Chicago, pp. 99-112.
2) Cuthbertson, D.P. (1929): The influence of prolonged muscular rest on metabolism. Biochem. J.,
3) Deitrick, J. E., Whedon, G. D., and Shorr, E. (1948): Effects of immobilization upon various metabolic and physiologic functions of normal men. *Am. J. Med.*, 4, 3–36.

4) Donaldson, C. L., Hulley S. B., Vogel, J. M., Hattrter, R. S., Boyers, J. H., and MacMillan, D. E. (1970): Effects of prolonged bed rest on bone mineral. *Metabolism*, 19, 1071–1084.

5) Whedon, G. D., and Shorr, E. (1957): Metabolic studies in paralytic acute anterior poliomyelitis. II. Alterations in calcium and phosphorus metabolism. *J. Clin. Invest.*, 36, 966–981.

6) Whedon, G. D., Lutwak, L., Reid, J., Rambaut, P., Whittle, M., Smith, M., and Leach, C. (1974): Mineral and nitrogen metabolic studies on Skylab orbital space flights. *Trans. Assoc. Am. Physicians*, 87, 95–110.

7) Vogel, J. M., and Whittle, M. W. (1976): Bone mineral content changes in the Skylab astronauts. *Am. J. Roentgenol. Radium Ther.*, *Nucl. Med.*, 126, 1296–1297.

8) Aloia J. F. (1981): Exercise and skeletal health. *J. Am. Geriatric Soc.*, 20, 104–107.

9) Smith, E. L., and Reddan, W. (1976): Physical activity—a modality for bone accretion in the aged. *Am. J. Roentgenol. Radium Ther.*, *Nucl. Med.*, 126, 1297.

10) Krolner, B., Toft, B., Nielsen, S. P., and Tondevold, E. (1983): Physical exercise as prophylaxis against involutional vertebral bone loss: a controlled trial. *Clin. Sci.*, 64, 541–546.

11) Dalen, N., and Olsson, K. E. (1974): Bone mineral content and physical activity. *Acta Orthop. Scand.*, 45, 170–174.

12) Nilsson, B., and Westlin, N. E. (1971): Bone density in athletes. *Clin. Orthopedics*, 77, 179–182.

13) Jacobson, P. C., Beaver, W., Grubb, S. A., Taft, T. N., and Talmage, R. V.: Bone density in women: college athletes and older athletic women. *J. Orthop. Res.*, in press.

14) Aloia, J. F., Cohn, S. H., Babu, T., Abesamis, T., Kalici, N., and Ellis, K. (1978): Skeletal mass and body composition in marathon runners. *Metabolism*, 27, 1793–1796.

15) Nilsson, B. E., and Westlin, N. E. (1971): Bone density in athletes. *Clin. Orthop. Rel. Res.*, 77, 179–182.

16) Donaldson, H. H. (1935): Summary of data for the effects of exercise on the organ weights of the albino rat: comparison with similar data from the dog. *Am. J. Anat.*, 56, 57–70.

17) Saville, P. D., and Whyte, M. P. (1969): Muscle and bone hypertrophy: positive effect of running exercise in the rat. *Clin. Orthopedics*, 65, 81–88.

18) Doyle, F., Brown, J., and LaChance, C. (1970): Relation between bone mass and muscle weight. *Lancet*, 1, 391–393.

19) Cohn, S. H. et al. (1976): Changes in body chemical composition with age measured by total body neutron activation. *Metabolism*, 25, 85–94.

20) Hantman, D. A., Vogel, J. M., Donaldson, C. L., Friedman, R., Goldsmith, R. S., and Hulley, S. B. (1973): Attempts to prevent disuse osteoporosis by treatment with calcitonin, longitudinal compression, and supplementary calcium and phosphates. *J. Clin. Endocrinol. Metab.*, 36, 845–858.

21) Schneider, V. S. and associates: unpublished studies.

22) Thornton, W.: Biomedical research studies on Skylab. NASA publication.

23) Whedon, G. D. (1984): Disuse osteoporosis: physiological aspects. *Calcif. Tissue Int.*, 36, S146–S150.

24) Cowin, S. C., Lanyon, L. E., and Rodan, G. (1984): Summary of discussion, Kroc Foundation Conference on Functional Adaptation in Bone Tissue. *Calcif. Tissue Int.*, 36, S4–S6.