Osteoporosis Int (1990) 1:56–60

Osteoporosis International

Hypothesis

Interaction of Genetic and Environmental Influences on Peak Bone Density

P. J. Kelly[1], J. A. Eisman[2] and P. N. Sambrook[3]

[1]Research Fellow and [2]Head, Bone and Mineral Research Division, Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, NSW 2010, Australia, and [3]Staff Specialist in Bone and Joint Disease, St. Vincent's Hospital, Sydney, NSW 2010, Australia

Abstract. Risk of osteoporotic fracture in later life relates to both age and menopause-related bone loss but also to peak bone density achieved in early adulthood. Several studies have shown that genetic influences make a major contribution to variance in adult bone density, but environmental factors such as dietary calcium and physical activity also contribute a large proportion of observed variance in bone density. Previous hypotheses have suggested that the effect of certain environmental factors, such as hormonal and dietary influences, may be permissive to development of peak bone mass. Consideration of the evidence for the interaction between environmental influences, such as physical activity and nutrition, and genotype leads us to propose that environmental factors interact to allow or prevent full expression of bone density genotype. This expansion of the 'threshold' hypothesis can include the effects of sex, physical activity and dietary calcium in a model that allows more systematic study of the determinants of peak bone density and thereby more rational intervention to augment bone density in early adulthood.

Keywords: Peak bone density; Bone density genotype; Dietary calcium intake

It is now well established that there are strong familial and genetic influences on adult bone density with genetic factors estimated to contribute around 80% of the total variance in bone density [1–6]. Analysis of twin data also suggest that a single gene or set of genes is responsible for this genetic effect [1]. These genetic studies imply that only a small amount of the variance in bone density could be due to environmental influences. However, several studies, including our own, have shown that physical fitness and strength may explain up to 40% of the variance in adult bone density [7]. Also recently we have found that dietary calcium may contribute up to 40% of the variance in bone density at the femoral neck in men [8]. It is unlikely, therefore, that these environmental and genetic effects are contributing independently. It has previously been proposed that peak bone density reflects the interplay between environmental and genetic factors [9]. In this concept, genetic factors may determine environmental factors through food preferences, and thus dietary calcium intake, or through predisposition to physical activity, and thus strength and physical fitness, as well as obvious effects on stature and body type.

With respect to dietary calcium intake, observations do not support a genetic effect [10]. Similarly, with respect to physical fitness or strength, twin studies have either failed to demonstrate a genetic effect (where fitness is expressed as predicted or measured maximal oxygen uptake per unit body weight), or found that any genetic effect is relatively weak [11–15]. Bouchard et al. have suggested from a twin and sibling study that genetic influences contribute only around 10% of the variance in VO_2 max corrected for lean body mass [16]. An alternative possibility is that environmental factors may be interlinked. By this concept physical activity could determine dietary intake and thus dietary calcium. However, strong relationships between dietary calcium intake and physical fitness have not been observed [17,18]. Therefore the data do not support the notion that genetic factors determine the environmental

Correspondence and offprint requests to: J. A. Eisman, Bone and Mineral Research Division, Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, NSW 2010, Australia.

influences or that the increased dietary intake of people who are more active results in a significantly greater intake of calcium. The hypothesis we have developed, from that initially put by Heaney [9], is that dietary calcium and physical activity are permissive factors that allow bone to reach its genotypic potential and that genotype determines the limit of skeletal response to environmental influences.

While the role of calcium and age- and menopause-related bone loss remains controversial, there is mounting evidence that calcium may be important in the attainment of peak adult bone density [19–24]. Bone density in premenopausal women has been found to be related to dietary calcium intake in young adulthood [19]. Others have shown that increasing dietary calcium intake from an average of 962 mg/day to 1336 mg/day may augment bone density at the lumbar spine in premenopausal women aged 30–40 years [23]. Also higher lumbar vertebral density (corrected for weight) has been observed in children with higher (>800 mg/day) dietary calcium intake suggesting a role for dietary calcium in the development of the skeleton through adolescence [24]. However, many other studies have failed to demonstrate a relationship between calcium intake and bone density in women. Riggs et al. [25] found no relationship between calcium intake and rates of change in bone density. The lack of relationship between bone density and current calcium intake may be due to lack of correspondence between past and current dietary calcium intake in women. We have recently found that dietary calcium was a strong independent predictor of bone density at both the lumbar spine and proximal femur in a group of normal men (median age 44 years) [8]. In this study dietary calcium explained 24% of the variance in bone density at the lumbar spine and 42% of the variance at the femoral neck. Interestingly, in children dietary calcium may predict bone mineral density in male twins but not in female twins [26]. Thus these data suggest that sex related differences *may* exist in the response to dietary calcium, although other factors such as stability of dietary intake may be more important.

One hypothesis to explain the effect of dietary calcium on peak bone density is that dietary calcium plays a permissive role allowing factors such as genetic potential or physical activity to exert their effects on the skeleton. Kanders et al. [27] found a relationship between dietary calcium intake, physical activity and bone density that supports this hypothesis. They found that vertebral bone density was significantly greater in a group of subjects with both greater daily energy expenditure (>970 kcal/day) and dietary calcium intake (>800 g/day). Also they [27] found a positive relationship between vertebral bone density and dietary calcium intake in those with calcium intakes less than 1000 mg/day, but not in those with higher dietary calcium intakes. Furthermore the strength of the relationship between dietary calcium intake and bone density was improved with the elimination of the effect of energy expenditure. While a recent study examining the effects of an exercise programme on postmenopausal women found no overall significant effect of exercise on vertebral bone loss there was a trend for the loss in the exercising group to be less in those with the greater dietary calcium intake [28]. In a study of the effect of calcium supplementation with 1500 mg calcium carbonate on bone loss in women, Smith and colleagues found that while the rate of loss from the left radius was no different to controls (mean dietary calcium intake 691 mg/day) the rate of loss was decreased by around 50% in the right (presumably dominant) radius of the treated subjects [29]. Block and co-workers found that in a group of exercising and non-exercising men there was a significant positive correlation between both paraspinous muscle area and dietary calcium intake and bone mineral density at the femoral neck [30]. However, in multiple regression analysis dietary calcium was not a predictor, independent of muscle area, of proximal femur bone mineral density, thus adding support to an interaction between calcium intake and physical activity on bone density.

Further evidence for an interrelated role of dietary calcium and physical activity on the attainment of peak adult bone mass comes from interesting anthropological observations. Eaton and Nelson have noted that the skeletal mass of humans from the Late Paleolithic age was greater than that of modern man [31]. While the level of physical activity was greater, so also was the dietary calcium intake, estimated to be twice that observed in modern Western societies. In the same review the authors point out that of hunter-gatherer populations, a group with a high level of physical activity, the only group with a prevalence of osteoporosis similar to that of modern Americans is the Inuit (Eskimos) who have a low dietary calcium intake. Therefore, it seems that the availability of calcium may play a permissive role in allowing the skeleton to respond to both genetic and other environmental influences such as physical activity.

From cross-sectional studies it is clear that there is a strong relationship between physical activity and strength and bone density in young adults. A number of studies have found that physical activity and physical fitness are predictors of bone mineral density at both the appendicular and axial skeleton. While we have suggested that a collaboration between activity and nutrition may exist there is also some challenging evidence to suggest that such an interplay may exist between genetics and adaptation to physical activity. Studies using the twin model have shown that changes in various metabolic parameters following physical training are genetically determined [32,33]. Despite the lack of evidence for a genetic effect on physical fitness in cross-sectional studies, the ability to increase physical fitness in response to physical activity may be genetically influenced [34]. Whether the response of bone to physical activity at various ages is genetically determined remains to be demonstrated. Furthermore, it is possible that certain genotypes may require greater environmental effects, i.e, greater physical training, to

attain their full genetic potential with respect to bone density. Further studies, particularly in twins, may be helpful in addressing this question.

There is evidence that sex may confound the relationship between bone density and environmental influences. Sex differences in bone mineral density at the appendicular skeleton have been observed with males having around 30% greater bone mineral density at the ultradistal and distal radius compared with females [35]. These data suggest that sex-related factors may have a skeletal site-specific effect. In a study of normal men we have found that an index of free testosterone was a positive predictor of bone mineral density at both the ultradistal and distal radius, while no such relationships was observed for the lumbar spine or femoral neck [8]. Furthermore studies in hypogonadal men treated with testosterone suggest that forearm bone may be more responsive to testosterone than axial bone [36–38]. Whether this relates to differences in the amount of cortical and trabecular bone at the various sites or reflects site-specific responsiveness or the effect of other environmental influences such as muscle strength remains to be determined. However, in contrast to the appendicular skeleton there is no evidence of sex-related differences in bone mineral density at the axial sites, despite the sex-related differences in body weight and muscle strength, both predictors of axial bone density [35]. Thus sex appears to have a site-specific effect, and for the axial skeleton female sex may override the influence of muscle strength or body weight.

We propose the hypothesis that dietary calcium intake may be most limiting in those with the greatest potential bone mass and that this potential may be determined by the interaction between genetic potential and other environmental factors such as exercise (see Fig. 1). Thus in individuals with the least genetic potential and the least positive influence from exercise, dietary calcium may be of limited benefit. In those with greater genetic potential amplified by positive environmental influences, otherwise adequate dietary calcium intakes may still be limiting. This relationship could be considered in the converse direction that, in those with least genetic potential and lowest dietary calcium intake, exercise may be relatively ineffective on bone mass. As an extension of this analysis, in those with the greatest genetic potential and in the presence of high dietary calcium intake, exercise may be able to achieve an optimal effect on bone mass. This hypothesis reasonably explains the conflicting data in the literature and the cumulative contributions of genetic and environmental factors apparently explaining more than 100% of observed variance as measured for bone density. This hypothesis would stress the importance of attention to all environmental factors in the achievement and maintenance of peak bone density.

Consideration of this hypothesis could lead to important modifications to experimental protocols. Generally investigations of the effects of calcium intake or of physical activity in cross-sectional studies have not controlled for these other potentially important factors. While efforts have usually been made to avoid individuals who have undertaken major lifestyle (diet or exercise) changes, more modest changes may have been overlooked. However levels of exercise or dietary intake could be expected to have changed quite substantially over the 10–20 years prior to most such studies, the time during which their effects on bone mass could be expected to have been exerted. We have proposed already that the failure to see a relationship between current dietary calcium intake in women (whereas we did find such a relationship in men [8]) may reflect greater variability in dietary intake over time. Even in prospective studies dietary calcium intake and exercise have seldom been evaluated as independent potential effectors. In studies of effects of calcium supplementation, possible changes in physical activity have not been monitored, or at least reported. In studies of effects of physical activity, dietary calcium intake has usually been increased by the addition of 1 g of calcium

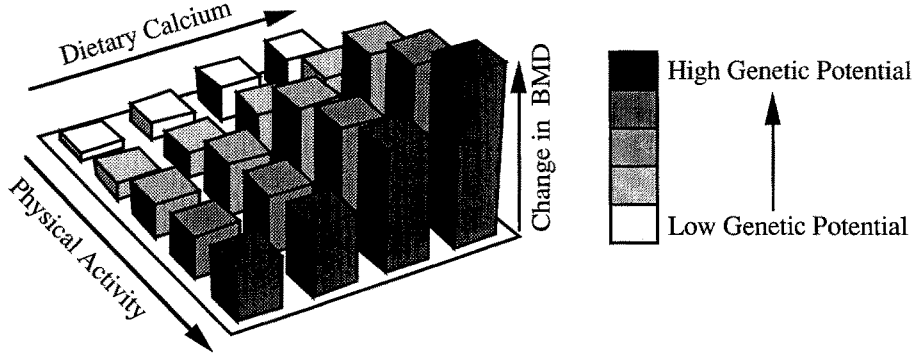

Fig. 1. Graphical representation of the proposed interactions between genetic potential, physical activity, dietary calcium and peak bone density. With low dietary calcium intakes the response to physical exercise is small and there is little difference between those with high and low genetic potential. As dietary calcium increases, the ability to increase bone mineral density in response to exercise and as allowed by the underlying genotype is augmented. With low levels of physical activity, the effect of dietary calcium intake and genetic potential may be masked. As physical activity increases the ability to increase bone density is determined by dietary calcium intake and genetic potential. The 'threshold' effect is still operative such that in individuals with high calcium intake or high levels of physical activity, further increases in those parameters would have little further effect.

daily. If the possible interactions of these environmental factors are to be evaluated in prospective studies, more careful experimental design must include unsupplemented calcium intake arms. Careful monitoring must be undertaken to ensure that the powerful media influences, advocating (perhaps quite reasonably) adequate calcium intakes, do not modify the intake in these individuals or at least that such changes are adequately recorded and can thus be evaluated. Evaluation of potential genetic factors is more difficult but the twin model is a powerful tool to examine such effects with the same sorts of monitoring mentioned above. The potential effects of these lifestyle factors must be considered in various prospective interventional studies of agents designed to prevent bone loss, e.g., sex hormone replacement and various other agents in the early postmenopausal state. The use of dietary questionnaires [39], simple questionnaires on physical activity or simple measures of fitness or strength could monitor such potential confounding factors and thus help to explain the at times contradictory results obtained in apparently similar studies.

In summary, there is mounting evidence to support the hypothesis of the interrelationship between environmental influences, in particular dietary calcium intake and physical activity, and genetic influences that determine the peak bone density achieved in young adulthood. Thus we propose that environmental factors interact with each other and their summed effects determine the extent to which bone density genotype is expressed. Closer examination of these relationships, particularly in prospective studies, could clarify these potential interactions and lead to more rational approaches to augmentation of peak bone density and therefore to prevention of osteoporosis.

References

1. Pocock NA, Eisman JA, Hopper JL, Yeates MG, Sambrook PN, Eberl S. Genetic determinants of bone mass in adults; a twin study. J Clin Invest 1987; 80: 706–10.
2. Evans RA, Marel GM, Lancaster EK et al. Bone mass is low in relatives of osteoporotic patients. Ann Intern Med 1988; 109: 870–3.
3. Dequeker J, Nijs J, Verstaeten A, Geusens P, Gevers G. Genetic determinants of bone mineral content at the spine and the radius: a twin study. Bone 1987; 8: 207–9.
4. Moller M, Horman A, Harvarld B, Hauge M, Henningsen K, Nordin BEC. Metacarpal morphometry in monozygotic and dizygotic elderly twins. Calcif Tissue Res 1978; 25: 197–201.
5. Smith DA, Nance WE, Won Kang K, Christian JC, Johnston CC Jr. Genetic factors in determining bone mass. J Clin Invest 1973; 52: 2800–8.
6. Seeman E, Hopper JL, Bach LA et al. Reduced bone mass in daughters of women with osteoporosis. New Engl J Med 1989; 320: 554–8.
7. Pocock NA, Eisman JA, Yeates MG, Sambrook PN, Eberl S. Physical fitness is a major determinant of femoral neck and lumbar spine bone mineral density, J Clin Invest 1986; 78: 618–21.
8. Kelly PJ, Pocock NA, Sambrook PN, Eisman JA. Dietary calcium, sex hormones and bone mineral density in men. Br Med J 1990; 300: 1361–4.
9. Heaney RP. Calcium, bone health and osteoporosis. In: Peck WA, ed. Bone and mineral research, vol. 4., Amsterdam: Elsevier 1986: 255–301.
10. Corey LA, Nance WE. A study of dietary intake in adult monozygotic twins. Acta Genet Med Gamellol 1980; 29: 263–71.
11. Howard H. Ultrastructure and biochemical function of skeletal muscle in twins. Ann Hum Biol 1976; 3: 455–62.
12. Komi PV, Viitasalo JT, Havu M, Thorstensson A, Karlsson J. Physiological and structural performance capacity: effect of heredity. In: Komi PV, ed. Biomechanics V, Baltimore, MD: University Park Press 1976; 118–23.
13. Lortie G, Bouchard C, LeBlanc A et al. Familial similarity in aerobic performance. Hum Biol 1982; 54: 801–12.
14. Lesage R, Simoneau JA, Jobin J, LeBlanc J, Bouchard C. Familial resemblance in maximal heart rate, blood lactate and aerobic power. Human Hered 1985; 35: 182–9.
15. Monotoye HJ, Gayle R. Familial relationships in maximal oxygen uptake. Hum Biol 1978; 50: 241–49.
16. Bouchard C, Lesage R, Lortie G et al. Aerobic performance in brothers, dizygotic and monozygotic twins. Med Sci Sports Exerc 1986; 18: 639–46.
17. Nelson ME, Meredith CN, Dawson-Hughes B, Evans WJ. Hormone and bone mineral status in endurance-trained and sedentary postmenopausal women. J Clin Endocrinol Metab 1988; 66: 927–33.
18. Orwoll ES, Ferar J, Oviatt SK, McClung MR, Huntington K. 1989; The relationship of swimming exercise to bone mass in men and women. Arch Int Med 1989; 149: 2197–200.
19. Picard D, Ste-Marie LG, Coutu D et al. Premenopausal bone mineral content relates to height, weight and calcium intake during early adulthood. Bone and Mineral 1988; 4: 299–309.
20. Elders PJM, Netelenbos JC, Lips P et al. Perimenopausal bone mass and risk factors. Bone and Mineral 1989; 7: 289–99.
21. Matkovic V, Kostial K, Siminovic I, Buzina R, Brodarec A, Nordin BEC. Bone status and fracture rates in two regions of Yugoslavia. Am J Clin Nutr 1979; 32: 540–9.
22. Sandler RB, Slemenda CW, LaPorte RE et al. Postmenopausal bone density and milk consumption in childhood and adolescence. Am J Clin Nutr 1985; 42: 270–4.
23. Baran D, Sorensen A, Grimes J et al. Dietary modification with dairy products for preventing vertebral bone loss in premenopausal women: A three-year study. J Clin Endocrinol Metab 1990; 70: 264–9.
24. Rubin KR, Schirduan VM, Gendreau P, Dalsky GP. Determinants of peak bone mass in healthy children and adolescence. J Bone Min Res 1989; Suppl 1: abstract 1024.
25. Riggs BL, Wahner HW, Melton LJ, Judd HL, O'Fallon WM. Dietary calcium intake and rates of bone loss in women. J Clin Invest 1987; 80: 979–82.
26. Johnston CC. Determinants of bone mass in the elderly. Proceedings of the fifth international Sydney bone symposium, Sydney, Australia, 1990.
27. Kanders B, Dempster DW, Lindsay R. Interaction of calcium nutrition and physical activity on bone mass in young women. J Bone Min Res 1988; 3: 145–9.
28. Sinaki M, Wahner HW, Offord KP, Hodgson SF. Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. Mayo Clin Proc 1989; 64: 762–9.
29. Smith EL, Gilligan C, Smith PE, Sempos CT. Calcium supplementation and bone loss in middle-aged women. Am J Clin Nutr 1989; 50: 833–42.
30. Block JE, Friedlander AL, Brooks GA, Steiger P, Stubbs HA, Gennat HK. Determinants of bone density among athletes engaged in weight-bearing and non-weight-bearing activity. J Appl Physiol 1989; 67: 1100–5.
31. Eaton SB, Nelson DA. Calcium in evolutionary perspective. Am J Clin Nutr (Suppl). In press.
32. Poehlman ET, Tremblay A, Marcotte, Perusse L, Theriault G, Bouchard C. Heredity and changes in body composition and adipose tissue metabolism after short-term exercise training. Eur J Appl Physiol 1987; 56: 398–402.
33. Depres JP, Bouchard C, Savard R, Prud-Homme D, Bukowiecki

L, Theriault G. Adaptive changes to training in adipose tissue lipolysis are genotype dependent. Int J Obesity 1984; 8: 87–95.
34. Klissouras V, Pirnay F, Petit J-M. Adaptation to maximal effort: genetics and age. J Appl Physiol 1973; 35: 288–93.
35. Kelly PJ, Twomey L, Sambrook PN, Eisman JA. Sex differences in peak adult bone density. J Bone Min Res 1990; 5 (in press).
36. Stepan JJ, Lachman L, Zverina J, Pacovsky V, Baylink D. Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodelling. J Clin Endocrinol Metab 1989; 69: 523–27.
37. Greenspan SL, Oppenheim DS, Klibanski A. Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. Ann Intern Med 1989; 110: 526–31.
38. Finkelstein JL, Klibanski A, Neer R et al. Increases in bone density during treatment of men with idiopathic hypogonadotrophic hypogonadism. J Clin Endocrinol Metab 1989; 69: 776–83.
39. Angus RM, Sambrook PN, Pocock NA, Eisman JA. A simple method for assessing calcium intake in caucasian women. J Am Diet Assoc 1989; 89: 209–14.