MINIREVIEW

Vitamin D in the Treatment of Osteoporosis Revisited* (43997)

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Abstract. **Interest in vitamin D treatment for osteoporosis has recently been revived because of the focus in various parts of the world on the elderly population, which is predominantly vitamin D deficient, in addition to postmenopausal osteoporosis due to estrogen withdrawal, which has been the central theme of osteoporosis research for many years. Combined use of other agents along with vitamin D has fortified the therapeutic armory against osteoporosis. The recent suggestion of a role of vitamin D receptor polymorphism in the development and progress of osteoporosis, possibly by interfering with its expected action, provoked intense discussions on the role of vitamin D in the pathogenesis and treatment of osteoporosis. Vitamin D receptor polymorphism may explain some of the racial differences in the incidence of osteoporosis and its complications. Responses to vitamin D treatment may also be predicted by vitamin D receptor allelic analysis, though the currently proposed allelic patterns are yet far from being widely accepted. The outlook for vitamin D treatment for osteoporosis may require insight into vitamin D receptor, not only for vitamin D's given form, but also for a possible future form designed to intervene at the genomic level.**
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Since the minireview "Vitamin D in the treatment of osteoporosis" (1) appeared, remarkable progress has been achieved in this field.

At the Consensus Developing Symposium after the 4th International Symposium on Osteoporosis in 1993, an agreement was reached on the therapeutic use of active forms of vitamin D and their derivatives as summarized below: (i) Adequate vitamin D supplement of 400–800 IU/day is necessary for elderly people, in view of the decrease of femoral neck fracture in response to vitamin D and calcium supplement. (ii) A low dose of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) along with calcium increases bone mineral density and decreases femoral neck fracture without causing significant hypercalcemia. (iii) Effects of vitamin D and its active forms should be compared and the need for combined use of vitamin D examined.

Evidence on vitamin D deficiency among the aging is accumulating with reference to osteoporosis, one of the major manifestation of aging. An age-bound decline is noted in dermal production of 7-dehydrocholesterol (2). Lower ultraviolet exposure causes a further decrease of dermal vitamin D biosynthesis (3), whereas regular solar exposure promotes it (4). Decline of kidney function in aging reduces renal production of 1,25(OH)$_2$D, and estrogen deficiency may accelerate this, in view of the impaired ability to synthesize calcitriol in response to parathyroid hormone (PTH). PTH secretion increases with age, causing secondary hyperparathyroidism of aging, probably as a result of insufficient feedback inhibition by calcium and calcitriol (5), and possibly acting as an important

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factor in bone loss in senile osteoporosis, as reported by many workers (6–10). High basal, maximal stimulated, and minimal nonsuppressible PTH in the elderly were readily normalized by a short-term $1,25(OH)_2D_3$ treatment (11). Decrease in the response of tissues to calcitriol may also be a factor in the development of osteoporosis (12). Aged gut may respond to vitamin D poorly (13, 14), which may be explained by a decrease of vitamin D receptors in the gut (15). Small doses of $1\alpha(OH)$ vitamin D_3 (0.5–1.0 μg) corrects calcium malabsorption changing the negative calcium balance in osteoporosis to a zero or a positive calcium balance, while vitamin D, which requires hydroxylation by the kidney, may not be able to do this because of the declining kidney function. Thus, the correlation between aging and bone loss appear to be closely related to vitamin D metabolism (16), though other factors such as immobilization may also be important and vitamin D deficiency may not be the only cause of bone loss in senility (17). Byme *et al.* (18) recommended low-dose (10–20 μg/day) vitamin D supplement for the treatment of osteoporosis.

Attention has been focused on possible defects in the reception side of the vitamin D action. Vitamin D receptor gene allele polymorphism was reported to be related to the hereditary risk for osteoporosis, a finding that has promoted extremely active discussion, as will be described in the second half of this review.

Osteoporosis in Vitamin D Deficiency in Old Age and Deficiency of Solar Exposure

Serum 1,25(OH)D (calcitriol) levels may decrease in women after menopause, and bone calcitriol levels are markedly decreased in aging and osteoporosis (19, 20). Controversial results have nevertheless been reported on the relationship between serum levels of vitamin D derivatives and bone mineral density, probably due to the varying racial, geographical, nutritional, and seasonal factors of the communities studied, as well as the physiological and pathological elements related to aging (21). Positive relationship may be associated with low vitamin D intake or low bone mineral density rather than high and replete vitamin D intake, suggesting the role of vitamin D as one of the threshold substances to maintain healthy bone.

Serum calcidiol levels, for instance, were closely correlated with bone mineral density in Spain (22). Luckert *et al.* partially prevented postmenopausal bone loss by vitamin D supplement (23). Though vitamin D or previtamin D has been thought to be adequately supplied throughout the world, the requirement of ultraviolet light for the conversion of previtamin D to vitamin D may be a trap. In an elderly population probably under inadequate solar exposure, Meunier *et al.* (24) and Chapuy *et al.* (25) found a supplement with 800 units of vitamin D along with 1.2 g of calcium daily effective in reducing the fracture rate. In a 3-year follow-up study conducted on 3270 ambulatory women with a mean age of 84 ± 6 years living in nursing homes, 1634 were given a supplement of 800 IU of vitamin D and 1.2 g of calcium as $CaPO_4$ daily, and 1636 were given a placebo. Between the 12th and 18th month of the study, 58 hip fractures were sustained in the placebo group, whereas only 38 fractures occurred in the vitamin D/calcium–supplemented group. BMD was higher, and serum PTH and alkaline phosphatase lower, in the supplemented group than in the control group.

Ooms *et al.* (26) tested the effect of 400 IU of vitamin D supplementation in 348 women older than 70 years over a period of 2 years. Bone mineral density at the femoral neck increased and serum PTH decreased with few side effects. A shorter solar exposure makes vitamin D deficiency more pronounced during winter, so vitamin D supplementation becomes especially effective winter to spring rather than summer to fall. According to Khaw *et al.*, a single dose of 100,000 IU (2.5 mg) of cholecalciferol raised serum 25-OH vitamin D and suppressed PTH by 12% in winter without a rise of serum calcium in a randomized double-blind study (27). Dawson-Hughes *et al.* (28) also conducted a double-blind, randomized 2-year trial of vitamin D supplement in healthy postmenopausal women residing at latitude 42°N and consuming an average of 100 IU of vitamin D. Either 100 or 700 IU of vitamin D supplement was given, along with 500 mg calcium. The group given 700 IU of vitamin D lost less bone than the group given 100 IU (1.06% ± 0.34% vs 2.54% ± 0.37% per year; $P = 0.003$), and 70% of the benefit occurred in winter to spring and 30% in summer to fall. In Finland, located farther north, Heikinheimo *et al.* (29) injecting 150,000 to 300,000 IU of vitamin D annually found a reduction in fractures in elderly men and women.

Vitamin D Therapy Combined with Other Agents

Estrogen therapy did not modify the effect of $1,25(OH)_2\ D_3$ as it suppressed PTH without raising parameters for bone resorption (30). Furthermore, Van Hoof *et al.* found an increase of serum $1,25(OH)_2D$ levels with estrogen or estrogen-progestin treatment, suggesting a synergistic action between estrogen and vitamin D (31). Serum $1,25(OH)_2D$ at 1, 6, 12, and 24 months of estrogen treatment was 130.5, 152.7, 170.8, and 155.2 p*M*, respectively.

Levels of calcium intake are important to ensure clinical effect and to avoid side effects in vitamin D therapy for osteoporosis. While high calcium intake along with a large dose of vitamin D may prompt side effects such as hypercalcemia and hypercalciuria, adequate calcium intake is necessary to achieve a positive effect. Menczel *et al.* treated 66 postmenopausal women with a mean age of 67 years with 1000 mg of calcium with or without 0.5 μg of 1α(OH) vitamin D_3 daily for 3 years (32). The group given 1α(OH) vitamin D_3 showed an increase of distal radius bone mineral density of 2%, whereas the control group with calcium alone lost 7.8%. Though hypercalciuria and mild and transient hypercalcemia occurred, no change in serum creatinine or creatinine clearance was found. Palmieri *et al.* found a combination of moderate-dose (less than 150 units/week) calcitonin and vitamin D effective in increasing trabecular bone mass and preventing the fall of cortical bone mass in osteoporosis (33). Fujita *et al.* (34) also administered 1 μg of 1α(OH) vitamin D_3/day orally with or without intramuscular injections of 20 unit/week elcatonin, an eel calcitonin derivative in a low-dose intermittent regimen, in elderly women with established osteoporosis. Vertebral fracture rate was significantly reduced in the group given 1α(OH) vitamin D_3 compared with the control group not taking the vitamin. Additional use of elcatonin further reduced the fracture rate markedly.

Vitamin D Receptor Polymorphism and Vitamin D Treatment

Development and clinical manifestations of osteoporosis is genetically influenced. The well-known gender and racial differences in the incidence of osteoporosis and its complications may have a genetic component. Smith *et al.* (35) first pointed out the genetic factors determining bone mass by demonstrating more similar BMD in monozygous twins than in dizygous ones, and Slemenda *et al.* (36) and Pocock *et al.* (37) confirmed it. Parameters controlling bone turnover, such as osteocalcin and type I collagen fragments, may also be influenced by genetic factors (38, 39). Morrison *et al.* in Australia pointed out a relationship between vitamin D receptor gene polymorphism and serum osteocalcin utilizing the responses to *Bsm* 1, *Apa* 1, and *Taq*l restriction enzymes (40), and went as far as suggesting the predictability of bone mineral density from vitamin D receptor alleles (41). According to these authors, polymorphism at the vitamin D receptor gene could explain 75% of the genetic effect on peak bone mass, and a 16% difference was found between subjects with different types of vitamin D receptor alleles. Husmyer *et al.*, however, found no relationship between these polymorphisms at the vitamin D receptor gene locus and spine, forearm, and femur BMD in their studies of 86 monozygotic and 39 dizygotic white adult female twins, though heritability seemed to account for over 70% of BMD (42). Furthermore, Garnero *et al.* (43, 44) found no relationship between the genotype for the three polymorphisms and bone formation and resorption markers or BMD in the spine, proximal femur, forearm, and whole body by DXA in 189 healthy premenopausal women between 31 and 57 years of age in France. Spector *et al.* conducted a study of white postmenopausal twins in the United Kingdom, which supported the original BMD–vitamin D receptor allele relationship concept in part (45). Gallagher *et al.* (46), Looney *et al.* (47), and Malhus *et al.* (48) also failed to confirm the concept. Kiel *et al.* (49) insisted on the significant relationship between vitamin D receptor polymorphism and BMD in younger subjects but denied it in older ones. Other studies are also conflicting (50–56). Peacock (57), summarizing these contrasting views, pointed out the need for linkage studies in races other than Caucasian of a very large number of subjects. Eisman defended the clinical relevance of vitamin D receptor gene polymorphism (58).

Races other than Caucasian may have entirely different patterns of vitamin D receptor alleles (59). In Japan, several investigators unanimously pointed out an extremely low frequency—one-tenth to one-fifth that in Caucasians—of BB-type alleles suggested by Morrison *et al.* to be osteoporosis prone (60–63). The lower incidence of hip fracture among Japanese than in Caucasians may be explained in part by the difference in vitamin D receptor allelic patterns. McClure *et al.* (64) found BB type in 8.7% of Mexican-American women, a value intermediate between Caucasians and Asians. Hayes *et al.* (65) found a longer femoral neck axis length, which has also been suggested to be responsible for hip fracture, more prevalent among subjects with TT-type vitamin D receptor alleles detected by *Taq* l restriction enzyme supposedly linked with the BB type.

The functional significance of vitamin D receptor allele polymorphism remains largely unknown. Gross *et al.* cultured dermal fibroblasts from subjects with vitamin D receptor allele type BB, and from those with type bb, and tested their response to $1,25(OH)_2D$ (66). No difference in binding to the receptor and induction of 24-hydroxylase mRNA was noted between the receptors from the two groups of subjects. Kinyamu *et al.* (67) studied the effect of age on calcium absorption, and its relationship with intestinal VDR and VDR genotypes. Allelic variation in VDR genotypes was not related to calcium absorption, serum $1,25(OH)_2D$ or intestinal VDR. Ferrari *et al.* (68) found a lower BMD in prepubital girls with BB genotypes of vitamin D receptor than in those with other types. Calcium supplementation increased bone mass accumulation in BB and Bb girls but not in bb girls who accumulated bone mass independent of calcium supplement, as seen in a follow-up of their study on VDR and BMD (69). Dawson-Hughes *et al.* (70) compared fractional calcium absorption in healthy late postmenopausal women with (bb) and without (BB) the Bsm 1 restriction site on both vitamin D receptor gene alleles. After 2 weeks of a high calcium intake of 1500 mg/day, calcium absorption index was similar in both groups. After 2 weeks of a low calcium intake of less than 300 mg/day, serum 1,25(OH) vitamin D increased similarly, but the increase of calcium absorption index was significantly greater in bb than in BB, suggesting a poorer adaptation to calcium restriction on account of the difference in the vitamin D receptor gene alleles. The lower incidence of BB in Japan may be explained by natural selection in response to thousands of years of exposure to low-calcium diet. Carling *et al.* (71) found higher bb types among patients with primary hyperparathyroidism. Calcium deficiency and secondary hyperparathyroidism may also cause a similar change in vitamin D receptor gene allele types. According to a study of elderly women with low calcium intake by Rosen *et al.* (72), correlation between serum osteocalcin and PTH, and between serum 25(OH) vitamin D and BMD, was found only in BB women, and serum osteocalcin was correlated with BMD only in bb women.

As to the response to vitamin D and VDR gene polymorphism, Howard *et al.* (73) found a significantly smaller increase of serum osteocalcin in response to 7-day administration of 2 μg of calcitriol in the BB group than in the bb group, and serum parathyroid hormone was also less suppressed in the BB group, suggesting a less favorable therapeutic response to vitamin D in the BB group. Matsuyama *et al.* (74, 75) demonstrated the best response of bone mineral density to oral administration of 1 μg of 1α(OH) vitamin D_3 in osteoporotic patients with bbaaTT VDR alleles followed by bbAaTT, BbAaTt, and BbAATt, in this order. Since the incidence of BB alleles is very low in Japan, only these four frequent haplotype combinations could be tested. Alleles b, T, and a seem to influence the response of vitamin D therapy in osteoporosis favorably, and B, t, and A unfavorably. Shiraki *et al.* (76) also found a more favorable response to vitamin D in osteoporotic patients with genotype aa than in those with AA. This may explain, at least in part, the variable responses to vitamin D therapy in osteoporosis among races, offering an explanation for the more beneficial effect of vitamin D derivatives on osteoporosis in Japan than in Western countries. Further studies along these lines are indicated, since vitamin D receptor gene allelic analysis may provide a valuable tool to guide the treatment of osteoporosis with vitamin D.

Summary

In addition to estrogen for postmenopausal osteoporosis, vitamin D and its active forms are used with increasing frequency in the treatment of primary osteoporosis, especially in those of higher age and under poor solar exposure. Combined use of other agents with different mechanisms of action may also widen the usefulness of vitamin D. Vitamin D receptor gene analysis with restriction enzymes has confirmed the importance of vitamin D in the pathogenesis of osteoporosis and may be of value in helping to decide on the indications for vitamin D treatment for osteoporosis, though serious questions regarding the physiologic and epidemiologic significance of currently suggested allelic patterns remain and are under active discussion.

1. Fujita T. Vitamin D in the treatment of osteoporosis. Proc Soc Exp Biol Med **199**:394–399, 1992.
2. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D_3. J Clin Invest **76**:1536–1538, 1985.
3. Bouillon RA, Auverx JH, Lissens WD, Palemans WK. Vitamin D status in the elderly: Season substrate deficiency causes 1,25-dihydroxy-cholecalciferol deficiency. Am J Clin Nutr **45**:755–763, 1987.
4. Reid IR, Gallagher DJA, Bosworth J. Prophylaxis against vitamin D deficiency in the elderly by regular sunlight exposure. Age Ageing **15**:35–40, 1986.
5. Silverberg SJ, Shane E, de la Cruz L. Abnormalities in parathyroid hormone secretion and 1,25-dihydroxyvitamin D formation in women with osteoporosis. N Engl J Med **320**:277–281, 1989.
6. Fujita T, Orimo H, Okano K, Yoshikawa M, Inoue T, Itami Y. Radioimmunoassay of serum parathyroid hormone in postmenopausal osteoporosis. Endocrinol Jpn **19**:571–577, 1972.
7. Wiske PS, Epstein S, Bell NH, Queener SF, Edmonson J, Johnston CC Jr. Increase in immunoreactive parathyroid hormone with age. N Engl J Med **300**:1419–1421, 1979.
8. Marcus R, Madvig P, Young G. Age-related changes in PTH and PTH action in normal humans. J Clin Endocrinol Metab **59**:223–230, 1984.
9. Orwoll ES, Meier DE. Alterations in calcium, vitamin D, and parathyroid hormone physiology in normal men with aging. J Clin Endocrinol Metab **63**:1262–1269, 1986.
10. Young P, Marcus R, Minkoff JR, Kim LY, Segre GV. Age-related rise in parathyroid hormone in man: The rise of intact and midmolecule antisera to distinguish hormone secretion from retention. J Bone Miner Res **2**:367–374, 1987.
11. Ledger GA, Burritt MF, Kao PC, O'Fallon WM, Riggs BL. Abnormalities of parathyroid hormone secretion in elderly women that are reversible by short term therapy with 1,25-dihydroxyvitamin D_3. J Clin Endocrinol Metab **79**:211–216, 1994.
12. Koren R, Ravid A, Liberman UA. Responsiveness to 1,25-dihydroxyvitamin D_3 is reduced in lymphocytes from osteoporotic women. J Bone Miner Res **7**:1057–1061, 1992.
13. Fransis RM, Peacock M, Taylor GA. Calcium malabsorption in elderly women with vertebral fractures. Evidence for resistance to the action of vitamin D metabolites on the bowel. Clin Sci **66**:103–107, 1984.
14. Gennari C, Agnesdei D, Nardi P. Estrogen preserves a normal responsiveness to 1,25-dihydroxyvitamin D_3 in oophrectomized women. J Clin Endocrinol Metab **71**:1288–1293, 1990.
15. Ebeling PR, Sandgren ME, DiMagno EP. Evidence of an age-related decrease in intestinal responsiveness to vitamin D: Relationship between serum 1,25-dihydroxyvitamin D and intestinal vitamin D receptor concentrations in normal women. J Clin Endocrinol Metab **75**:176–182, 1992.
16. Bell NH. Vitamin D metabolism, aging and bone loss. J Clin Endocrinol Metab **60**:1051, 1995.
17. Sorva A, Välimäki M, Risteli J, Risteli L, Elfving S, Takkunen H, Tilvis R. Serum ionized calcium, intact PTH and novel mark-

ers of bone turnover in bedridden elderly patients. Eur J Clin Invest **24**:806–812, 1994.
18. Byme PM, Frearney R, McKenna MJ. Vitamin D supplementation in the elderly: Review of safety and effectiveness of different regimes. Calcif Tissue Int **56**:518–520, 1995.
19. Sagiv P, Lidor C, Hallel T, Edelstein P. Decrease in bone level of 1,25-dihydroxyvitamin D in women over 45 years old. Calcif Tissue Int **51**:24–26, 1992.
20. Lidor C, Sagiv P, Amdur B. Decrease in bone levels of 1,25-dihydroxyvitamin D in women with subcapital fracture of the femur. Proc 4th International Symposium on Osteoporosis and Consensus Development Conference, pp11–12, 1993.
21. Martinez ME, del Campo MT, Sanchez-Cabezudo MJ, Garcia JA, Calvin MTS, Torrijos A, Coya A, Munuera L. Relation between calcidiol serum levels and bone mineral density in postmenopausal women with low bone density. Calcif Tissue Int **55**:253–256, 1994.
22. Bikle DD. Role of vitamin D, its metabolites, and analogs in the management of osteoporosis. Rheum Dis Clin North Am **20**:759–775, 1994.
23. Lukert B, Higgins J, Stoskopf M. Menopausal bone loss is partially regulated by dietary intake of vitamin D. Calcif Tissue Int **51**:173–179, 1992.
24. Meunier PJ, Chapuy MC, Arlot PD, Delmas P, Dubboeur F, Brun J, Crouzet B, Arnaud S. Effects of a calcium and vitamin D_3 supplement on non-vertebral fracture rate, femoral bone density and parathyroid function in elderly women. A prospective placebo-controlled study. J Bone Miner Res **6**(Suppl 1):135, 1991.
25. Chapuy MC, Arlot ME, Dubbouer F. Vitamin D_3 and calcium to prevent hip fracture. N Engl J Med **327**:1637–1642, 1992.
26. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJF, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: A randomized double-blind trial. J Clin Endocrinol Metab **80**:1052–1058, 1995.
27. Khaw K-T, Scragg R, Murphy S. Single dose cholecalciferol suppresses the winter increase in parathyroid hormone concentration in healthy older men and women: A randomized trial. Am J Clin Nutr **59**:1040–1044, 1994.
28. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rate of bone loss in postmenopausal women randomly assigned to one of the dosages of vitamin D. Am J Clin Nutr **61**:1140–1145, 1995.
29. Heikinheimo JR, Inkovaara JA, Harju JE. Annual injection of vitamin D and fracture of aged bones. Calcif Tissue Int **51**:105–110, 1992.
30. Cosman F, Nieves J, Shen V, Lindsay R. Oral 1,25-dihydroxyvitamin D administration in osteoporotic women: Effect of estrogen therapy. J Bone Miner Res **10**:594–600, 1995.
31. Van Hoof HJ, van der Mooren MJ, Swinkels LM, Rolland R, Benraad TJ. Hormone replacement therapy increases serum 1,25-dihydroxyvitamin D: A 2 year prospective study. Calcif Tissue Int **55**:417–419, 1994.
32. Menczel J, Foldes J, Steinberg R, Leichter I, Shalita B, Bdolah-Abram T, Kadosh S, Mazor Z, Ladkani D. Alfacalcidol (Alpha D_3) in osteoporosis. Clin Orthop Related Res **300**:241–247, 1994.
33. Palmieri GMA, Pitcock JA, Brown P, Karas JG, Roen LJ. Effect of calcitonin and vitamin D in osteoporosis. Calcif Tissue Int **45**:137–141, 1989.
34. Fujita T, Fukase M, Shimada T, Yamamoto H. Treatment of established osteoporosis with 1α(OH) vitamin D_3 and low dose intermittent elcatonin, eel calcitonin derivative. J Bone Miner Metab **10**:37–40, 1992.
35. Smith DA, Nance WE, Wong Kang K, Christian JC, Johnston CC Jr. Genetic factors determining bone mass. J Clin Invest **52**:2800–2808, 1973.
36. Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnston CC Jr. Genetic determinants of bone mass in adult women: A reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. J Bone Miner Res **6**:561–567,1991.
37. Pocock NA, Eisman JA, Hopper JL, Yeates, MG, Sambrook PN, Ebert S. Genetic factors in bone mass in adults. A twin study. J Clin Invest **80**:706–710, 1987.
38. Kelly PJ, Hopper JL, Macaskill GT, Pocock NA, Sambrook PN, Eisman JA. Genetic factors in bone turnover. J Clin Endocrinol Metab **72**:808–814, 1991.
39. Tokita A, Kelly PJ, Nguyen TU, Qi JC, Morrison NA, Risteli L, Sambrook PN, Eisman JA. Genetic influences on type I collagen synthesis and degradation: Further evidence for genetic regulation of bone turnover. J Clin Endocrinol Metab **78**:1461–1466, 1994.
40. Morrison NA, Yeoman R, Kelly PJ, Eisman JA. Contribution of transacting factor alleles to normal physiological variability: Vitamin D receptor gene polymorphisms and circulating osteocalcin. Proc Nat Acad Sci USA **89**:6665–6669, 1992.
41. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN, Eisman JA. Prediction of bone density by vitamin D receptor alleles. Nature **367**:284–287, 1994.
42. Hustmyer FG, Peacock M, Hui S, Johnston CC Jr., Christian C. Bone mineral density in relation to polymorphism at the vitamin D receptor gene locus. J Clin Invest **94**:2130–2134, 1994.
43. Ganero P, Borel O, Sornay-Rendu E, Delmas PD. Vitamin D receptor gene polymorphisms do not predict bone turnover and bone mass in healthy premenopausal women. J Bone Miner Metab **10**:1283–1287, 1995.
44. Ganero P, Borel O, Sonay-Rendu E, Arlot ME, Delmas PE. Vitamin D receptor gene polymorphisms do not predict peal bone mass, postmenopausal bone loss and bone turnover, The Ofely study. (abstract) J Bone Miner Metab **10**(Suppl 1):S161, 1995.
45. Spector TD, Keen RW, Arden NK, Major PJ, Baker JR, Morrison NA, Nguyen TV, Kelly PJ, Sambrook PN, Lanchbury JS, Eisman JA. Vitamin D receptor alleles and bone density in postmenopausal women: A UK twin study. Br J Med **310**:1357–1360, 1995.
46. Gallagher JC, Goldgar D, Kinyamu H, Fannon P. Vitamin D receptor genotypes in Type I osteoporosis. (abstract) J Bone Miner Res **9**(Suppl 1):143, 1994.
47. Looney JE, Yoon H, Fischer M, Farley SM, Farley JR, Wergedal JE, Baylink DJ. Lack of high prevalence of the BB vitamin D genotype in severely osteoporotic women. J Clin Endocrinol Metab **80**:2158–2162, 1995.
48. Melhus H, Kindmark A, Amér S, Wilén B, Linch E, Ljunghall S. Vitamin D receptor genotypes in osteoporosis. Lancet **344**:949–950, 1994.
49. Kiel DP, Kong XF, Zhu XH, Ordovas J, Felson DT, Myers RH, Eisman JA, Sambrook PN, Nguyen TV, Holick MF. Polymorphism at the vitamin D receptor (VDR) are associated with bone mineral density (BMD) in younger but not older persons. (abstract) J Bone Miner Res **10**(Suppl 1):S189, 1995.
50. Peacock M, Hustmyer FG, Johnston CC Jr., Christian J. Heritability of bone mass, bone turnover, calcium regulation and calcium absorption in relation to RFLP at the vitamin D and PTH receptor gene. (abstract) Bone **16**(Suppl 1):83, 1995.
51. Kröger H, Mahonen A, Ryhänen S, Turunen AM, Alhava E, Mäenpää P. Vitamin D genotypes and bone mineral density. Lancet **345**:1238, 1995.
52. Fleet JC, Harris SS, Wood RJ, Dawson-Hughes B. The BsmI vitamin D receptor restriction fragment length polymorphism (BB) predicts low bone density in premenopausal black and white women. J Bone Miner Res **10**:985–990, 1995.
53. Riggs BL, Nguyen TV, Melton LJ III, Morrison NA, O'Fallon WM, Kelly PJ, Egan KS, Sambrook PN, Muhs JM, Eisman JA.

The contribution of vitamin D receptor gene alleles to the determination of bone mineral density in normal and osteoporotic women. J Bone Miner Res **10**:991–996, 1995.
54. Krall EA, Parry P, Lichter JB, Dawson-Hughes B. Vitamin D receptor alleles and rates of bone loss: Influence of years after menopause and calcium intake. J Bone Miner Res **10**:978–984, 1995.
55. Klisovic D, Young AP, Ilich JZ, Skugor M, Badenhop N, Matkovic V: Vitamin D receptor gene polymorphism (VDR) and bone mineral density (BMD) in prepuberal females. J Bone Miner Res **10**(Suppl 1):S189, 1995.
56. Shøller J, Jørgensen HL, Sand JC, Jensen M, Hassager C, Christiansen C. The impact of common allelic variation at the vitamin D receptor locus on bone mass is not clinically relevant. (abstract) J Bone Miner Metab **10**(Suppl 1):S161, 1995.
57. Peacock M. Vitamin D receptor gene alleles and osteoporosis: A contrasting view. J Bone Miner Res **10**:1294–1297, 1995.
58. Eisman JA. Vitamin D receptor gene alleles and osteoporosis: An affirmative view. J Bone Miner Res **10**:1289–1293, 1995.
59. Hustmyer FG, DeLuca HF, Peacock M. *ApaI*, *BsmI*, *Eco* RV and *TaqI* polymorphism at the human vitamin D receptor gene locus in Caucasians, blacks and Asians. Hum Mol Genet **2**:487, 1993.
60. Yamagata Z, Miyamura T, Iijima S, Asaka A, Sasaki M, Kato J, Koizumi K. Vitamin D receptor gene polymorphism and bone mineral density in healthy Japanese women. Lancet **344**:1027, 1994.
61. Shiraki M, Eguchi H, Aoki C, Shiraki Y. Can allelic variations in vitamin D receptor gene predict bone densities and serum osteocalcin level in Japanese women. (abstract) Bone **16**(Suppl 1):84, 1995.
62. Tokita A, Watanabe T, Miura Y, Tawa T, Yabuta K, Matsumoto H, Yamamori S, Morrison NA, Eisman JA. Vitamin D receptor gene RFLP and bone mineral density in Japanese. Bone (abstract) **16**(Suppl 1):83, 1995.
63. Miura Y, Tokita A, Tawa T, Maruyama T, Shira Y, Oyanagi M, Yabuta K. The effect of vitamin D receptor alleles and exercise on peak bone density in Japanese. (abstract) J Bone Miner Res **10**:(Suppl 1):S187, 1995.
64. McClure L, Gross C, Villa ML, Eccleshall R, Lin N, Kohlmeier L, Kelsey J, Marcus R, Feldman D. Vitamin D receptor alleles, bone mineral density, and bone metabolism in elderly Mexican-American women. (abstract) J Bone Miner Res **10**(Suppl 1):S189, 1995.
65. Hayes JG, Nguyen TV, Kelly PJ, Oi JC, Morrison NA, Peacock NA, Sambrook PN, Eisman JA. Vitamin D receptor alleles and femoral neck axis length. (abstract) J Bone Miner Res **10**(Suppl 1):93, 1995.
66. Gross C, Musiol I, Ecclesiall R, Malloy PJ, Feldman D. Vitamin D receptor (VDR) alleles. Study of VDR expression and function in cultured human skin fibroblasts. (abstract) J Bone Miner Res **10**(Suppl 1):S162, 1995.
67. Kinyamu H, Gallagher JC, DeLuca HF, Prahl J, Lanspa S, Knezetic J, Agarwal R. Relationship between intestinal vitamin D receptor, VDR genotypes, calcium absorption, and serum $1,25(OH)_2D$ in normal women. (abstract) J Bone Miner Res **10**(Suppl 1):S14, 1995.
68. Ferrari SL, Rizzoli R, Theintz G, Slosman DO, Bonjour JP. Vitamin D receptor (VDR) gene polymorphisms and the effects of calcium supplementation on bone mass accumulation in prepubital girls. J Bone Miner Res **10**(Suppl 1):S187, 1995.
69. Ferrari S, Rizzoli R, Chevalley T, Slosman D, Eisman JA, Bonjour JP. Vitamin D receptor gene polymorphisms and change in lumbar spine bone mineral density. Lancet **345**:990, 1995.
70. Dawson-Hughes B, Harris SS, Fineran S. Calcium absorption on high and low calcium intakes in relation to vitamin D receptor genotype. J Bone Miner Res **10**(Suppl 1):S14, 1995.
71. Carling T, Kindmark A, Hellman P, Ridefelt P, Ljunghall S, Rastad J, Åkerström G, Melhus H. Vitamin D receptor genotypes in primary hyperparthyroidism. (abstract) J Bone Miner Res **10**(Suppl 1):S187, 1995.
72. Rosen CJ, Vereault D, Holick MF, Rogers J, Witte SM. Functional significance of VDR genotypes in elderly women with low calcium intake. J Bone Miner Res **10**(Suppl 1):S186, 1995.
73. Howard G, Nguyen T, Morrison N, Watanabe T, Sambrook P, Eisman JA, Kelly PJ. Genetic influence on bone density: Physiological correlates of vitamin D receptor gene alleles in premenopausal women. J Clin Endocrinol Metab **80**:2800–2805, 1995.
74. Matsuyama T, Ishii S, Tokita A, Yabuta K, Yamamori S, Morrison NA, Eisman JA. Vitamin D receptor genotypes and bone mineral density. Lancet **345**:1238–1239, 1995.
75. Matsuyama T, Tokita A, Yabuta K, Yamamori S, Ishii S. Response to vitamin D treatment and alleles of vitamin D receptor gene in osteoporotic subjects. (abstract) J Bone Miner Res **10**(Suppl 1):S26,1995.
76. Shiraki M, Shiraki Y, Aoki C, Eguchi H. Genotypes of vitamin D receptor gene and response to vitamin D_3 treatment in postmenopausal osteoporosis. (abstract) J Bone Miner Res **10**(Suppl 1):S187, 1995.