# Vitamin D Receptor Genotype and the Risk of Bone Fractures in Women

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Several studies have confirmed an initial report of a relation between bone density and polymorphic forms of the calcitriol (vitamin D) receptor gene, whereas others have failed to find an association. We examined whether variants of the vitamin D receptor gene are associated with the risk of bone fracture, using a nested case-control analysis within the Nurses' Health Study cohort. The study women all were Caucasian and were 43–69 years of age when they provided a blood sample. Cases included the 54 proximal femur (hip) fractures and 163 distal radius (forearm) fractures that occurred subsequent to the blood draw. Cases and controls were genotyped by polymerase chain reaction for the *Bsm*I polymorphism. The *BB* genotype, previously associated with lower bone density, was associated with a more than twofold increased risk of hip fracture compared with the *bb* genotype. Risk was greater for women who were older, leaner, or less physically active or who had a lower calcium intake. The heterozygous genotype was not associated with any increased risk of hip fracture, and we observed little association between vitamin D receptor genotype and forearm fracture. This study supports an association between vitamin D receptor genotype and hip fracture. It also implies that modification by other risk factors may have contributed to the conflicting results from previous studies of vitamin D receptor genotype and femoral bone density. (Epidemiology 1998;9: 535–539)

**Keywords: bone, calcitriol receptor, genotype, hip fractures, radius fractures, vitamin D.**

Heredity is a substantial determinant of peak bone mass. Studies among twins[1,2] and among mother/daughter pairs[3,4] suggest that up to 80% of the age-specific variation in bone density may be genetically determined. Morrison *et al*[5] generated much interest in certain allelic variants of the gene encoding the vitamin D receptor (*VDR*) when they demonstrated a strong association between these variants and bone density at the spine and proximal femur among Australian twins. They also reported that the *VDR* alleles could predict differences of about one standard deviation in bone density in a cross-sectional study of unrelated postmenopausal women. A subsequent twin study with postmenopausal British women[6] provided support for an association between the *VDR* alleles and bone density at the femoral neck, whereas data from a twin study of U.S. women[7] found no evidence that the *VDR* gene was related to bone density at the lumbar spine, femoral neck, or distal radius. More uncertainty has been generated by the recent statement that the findings of Morrison *et al*[8] from their original twin study were weakened after further analyses by the same authors, although the results of their cross-sectional study were unchanged.

Despite this, numerous studies have found associations between the *VDR* genotypes and bone mineral density,[9-14] rates of bone loss,[9,15,16] hip geometry,[17] and calcium absorption.[18,19] Others, however, have not observed these associations.[20-28] A meta-analysis[29] found enough evidence to support a reduction in femoral, spinal, and radial bone mineral densities in the *BB* compared with the *bb* genotype groups, although the reduction was much more modest than that originally reported by Morrison *et al.*[5] Thus, the importance of the *VDR* receptor genotype for bone density and osteoporosis remains controversial.[30,31] Discrepancies in study results may be due to racial differences or the influence of unmeasured environmental factors.

Little is known about the effect of *VDR* genotype on fracture risk. Comparisons between osteoporotic women with fractures and nonosteoporotic controls have generally failed to find differences in *VDR* genotype.[23,32-35] One prospective analysis from the Dubbo Osteoporosis Epidemiology Study[36] did find an association between atraumatic fracture rate and *VDR* genotype that was most pronounced among women with low femoral bone

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Supported by Research Grants AR41383, CA40356, and CA49449 from the National Institutes of Health.

Submitted November 22, 1996; final version accepted February 23, 1998.

density. Still, these investigations did not adequately consider the role of other factors that are strong predictors of bone fracture. Therefore, we tested the hypothesis that *VDR* genotype affects the risk of hip and distal forearm fractures in women from the Nurses' Health Study (NHS) cohort, and we examined whether these associations are modified by age, body mass index, physical activity, or calcium intake.

## Subjects and Methods

### Cases and Controls

The NHS is a longitudinal investigation that was begun in 1976 with 121,701 female nurses 30–55 years of age. Every 2 years, the women receive a questionnaire that asks about current life-style behaviors and health status. Participants who report a hip or forearm fracture are asked for the date of occurrence, circumstances, and exact bone site. Only first-reported fractures of the proximal femur (hip) and distal radius (forearm) due to low or moderate trauma were considered as possible cases for this analysis. About 25% of the cases experienced high-trauma events (for example, motor vehicle accidents, skiing, horseback riding, or falling off a ladder) and were therefore excluded from analysis.

In 1989 and 1990, we received blood samples from 32,826 NHS participants. For a parallel study of endogenous sex hormones and fractures, we identified 54 incident hip fractures and 169 incident forearm fractures among Caucasian women who were free of diagnosed cancer. These women ranged from 43 to 69 years of age at the time of their blood draw. One control was matched to each forearm fracture case, and two controls were matched to each hip fracture case on age at blood draw, month of blood draw, and menopausal status (premenopausal, postmenopausal, or dubious status). Postmenopausal women were further matched on age at menopause, reason for menopause (natural or removal of two ovaries, or removal of one ovary and/or uterus), and use of estrogen replacement therapy (current, past, or never).

### Laboratory Methods

The *VDR* genotype was determined by polymerase chain reaction (PCR) amplification on stored buffy coat samples using a modification of the method of Morrison *et al.*[5] The PCR products were digested with the endonuclease *Bsm*I, and the banding patterns were determined as follows: homozygotes lacking the *Bsm*I site (*BB*) resulted in one undigested fragment of 810 base pairs; homozygotes with the *Bsm*I site (*bb*) produced two fragments of 620 and 190 base pairs; and heterozygotes (*Bb*) yielded three fragments of 810, 620, and 190 base pairs. Two forearm fracture cases and four controls were not genotyped owing to technical difficulty.

To test laboratory reproducibility, replicate aliquots from 10 different subjects were included with the case and control samples. The laboratory technician was blinded to case, control, and replicate status. All replicates from the same subject were identified as having concordant *VDR* genotypes.

### Questionnaire Data

Body mass index [weight (kg) per height squared ($m^2$)] was calculated from weight reported at the time of blood draw and height reported on the initial 1976 NHS questionnaire. Physical activity was assessed on the 1988 NHS questionnaire from a list of eight leisure-time activities, including walking, aerobic exercise, and various sports.[37] Activity was measured in units of metabolic equivalents (mets), where 1 met is equal to 1 hour of sitting quietly. Daily nutrient intakes from foods and supplements were measured with a food frequency questionnaire in 1986.[38]

### Statistical Analysis

In conditional logistic regression analyses, we calculated relative risks [RRs] to compare the risks for hip and forearm fracture among women with the *BB*, *Bb*, and *bb* genotypes. Body mass index, physical activity, and dietary intakes of calcium, vitamin D, protein, alcohol, and caffeine were included in multivariate models. We then stratified these analyses by age at fracture to examine whether age modifies the associations between genotype and fracture risk. We used the median ages at hip and forearm fracture as cutpoints for stratification.

We re-analyzed the hip and forearm fracture cases and controls using unmatched logistic regression analyses adjusted for age at blood draw. Because the resulting RRs were very similar to those from the conditional analyses, we proceeded with further unmatched analyses stratified by body mass index, physical activity, and calcium intake to explore the possibility that associations between *VDR* genotype and risks of hip and forearm fracture are modified by environmental factors. Median values were used as cutpoints for stratification.

## Results

Characteristics of the study population by case/control status are shown in Table 1. Cases and controls were similar in all characteristics except for a lower body mass index and higher alcohol consumption among hip fracture cases compared with controls. Mean alcohol intake was also higher in the *bb* genotype group compared with the *BB* group (data not shown). Eighty-nine per cent of the hip fracture cases and controls and 76% of the forearm fracture cases and controls were postmenopausal at the time of their blood draw, and about one-third of these postmenopausal women were currently on estrogen therapy.

*VDR* genotype frequencies were very similar in the forearm fracture cases and controls. In contrast, the *BB* genotype was present in 30% of the hip fracture cases but in only 15% of the controls. Both hip and forearm fracture cases and controls were in Hardy-Weinberg equilibrium.

In conditional logistic regression analyses, the risk of hip fracture was increased [RR = 2.23; 95% confidence

**TABLE 1. Characteristics of the Study Population by Fracture Case/Control Status**

| | Hip | | Forearm | |
|---|---|---|---|---|
| | Cases (N = 54) | Controls (N = 108) | Cases (N = 163) | Controls (N = 163) |
| | *Number (%)* | | | |
| VDR genotype | | | | |
| *BB* | 16 (30) | 16 (15) | 25 (15) | 26 (16) |
| *Bb* | 21 (39) | 53 (49) | 83 (51) | 89 (55) |
| *bb* | 17 (31) | 39 (36) | 55 (34) | 48 (29) |
| Postmenopausal* | 48 (89) | 96 (89) | 123 (76) | 123 (76) |
| Current estrogen user*,† | 16 (33) | 32 (33) | 39 (32) | 39 (32) |
| | *Mean ± Standard Deviation* | | | |
| Age at blood draw* (years) | 62.3 ± 5.7 | 62.2 ± 5.7 | 58.3 ± 6.8 | 58.1 ± 6.7 |
| Age at menopause*,† (years) | 48.5 ± 4.3 | 48.6 ± 4.2 | 47.3 ± 5.8 | 47.3 ± 5.7 |
| Body mass index (kg/m$^2$) | 23.0 ± 3.2 | 26.2 ± 5.3 | 25.3 ± 4.3 | 26.0 ± 5.5 |
| Physical activity‡ (mets/week) | 15.1 ± 16 | 16.4 ± 18 | 14.3 ± 16 | 14.2 ± 16 |
| Nutrient intakes§ per day: | | | | |
| Calcium (mg) | 1206 ± 562 | 1115 ± 470 | 1152 ± 507 | 1155 ± 517 |
| Vitamin D (IU) | 379 ± 308 | 355 ± 245 | 364 ± 293 | 326 ± 271 |
| Protein (gm) | 71 ± 15 | 75 ± 14 | 73 ± 12 | 75 ± 13 |
| Alcohol (gm) | 9.8 ± 17 | 7.0 ± 9 | 7.1 ± 11 | 7.1 ± 11 |
| Caffeine (mg) | 238 ± 177 | 246 ± 194 | 297 ± 227 | 291 ± 245 |

* Matching factors for cases and controls.
† Current estrogen use and age at menopause were assessed among postmenopausal women only.
‡ Measured in units of metabolic equivalents (1 met = the energy expenditure from 1 hour of sitting); met scores were missing for 1 hip control, 1 wrist case, and 1 wrist control.
§ Nutrient data were missing for 4 hip cases, 8 hip controls, 24 forearm cases, and 22 forearm controls.

interval (CI) = 0.91–5.46] among women with the *BB* genotype compared with those with the *bb* genotype (Table 2). The addition of body mass index, physical activity, calcium intake, and alcohol consumption to the regression model raised the effect estimate slightly. The further addition of vitamin D, protein, and caffeine intakes had little effect on the results. Because the heterozygous allele did not confer any additional risk, we re-analyzed the data with a reference group that included both the *Bb* and *bb* genotypes. In this analysis, women with the *BB* genotype had an RR of 2.35 (95% CI = 1.07–5.16) in the unadjusted model for hip fracture. When the covariates listed above were included in the model, the RR increased slightly.

This increased risk of hip fracture appeared to be modified by several factors (Table 3). No appreciable increase in fracture risk was observed among case/control pairs in which the case was less than 66 years old at fracture, whereas case/control pairs with an older age at fracture experienced an almost fourfold increase in risk. The *BB* genotype was also associated with large increases in risk of hip fracture among women with a body mass index less than 24.2 kg/m$^2$, a physical activity score less than 10.2 mets per week (equivalent to about 3.5 hours of walking or 1.5 hours of jogging), or a calcium intake less than 1,078 mg/day, whereas no appreciable increases in risk were apparent for leaner or less active women or for those with higher calcium intakes.

In contrast to the results for hip fracture, the *BB* genotype was not associated with an increased risk of distal forearm fractures (Table 2). We also found no evidence that the association was modified by any of the measured covariates.

**TABLE 2. Relative Risks (RR) and 95% Confidence Intervals (CI) for Hip and Forearm Fractures by Genotype of the Vitamin D Receptor**

| | Hip | | Forearm | |
|---|---|---|---|---|
| | RR | (95% CI) | RR | (95% CI) |
| *BB vs bb* | | | | |
| Unadjusted* | 2.23 | (0.91–5.46) | 0.83 | (0.42–1.65) |
| Multivariate† | 2.40 | (0.84–6.89) | 0.77 | (0.37–1.58) |
| *Bb vs bb* | | | | |
| Unadjusted | 0.92 | (0.44–1.93) | 0.82 | (0.51–1.32) |
| Multivariate | 0.92 | (0.39–2.15) | 0.84 | (0.51–1.38) |
| *BB vs Bb* | | | | |
| Unadjusted | 2.44 | (1.04–5.69) | 1.02 | (0.55–1.87) |
| Multivariate | 2.62 | (0.94–7.31) | 0.91 | (0.48–1.75) |

* Conditional logistic regression analyses with cases and controls matched on age at blood draw, month of blood draw, and menopausal status; postmenopausal women were further matched on age at menopause, reason for menopause, and use of postmenopausal estrogen.
† Conditional logistic regression models were adjusted for body mass index, physical activity, calcium intake, and alcohol consumption.

## Discussion

In this cohort of women, the *BB* allele of the *VDR* gene was associated with an increased risk of hip fracture. Our results are consistent with previous findings of decreased femoral bone density among women with this genotype.[5,6,10,32] We also found no increased risk of hip fracture associated with the heterozygous genotype. Consistent with our results, Fleet *et al*[10] observed little difference in femoral bone density between the *Bb* and *bb* genotypes, whereas both were associated with higher densities than was the *BB* genotype. Morrison *et al*[5] and Riggs *et al*,[32] however, observed a stepwise progression in femoral bone density over the three genotypes.

In contrast with our results for hip fractures, we did not find an association between *VDR* genotype and the risk of distal forearm fractures in this same cohort of women. In support of these discrepant results, Spector *et al*[6] found an association between *VDR* genotype and bone mineral density at the hip but not at the radius. Differences in bone composition and the importance of other risk factors for fractures at these two sites may partially explain the inconsistent associations.

The increased risk of hip fracture associated with the *BB* genotype became more pronounced with an older age at fracture. This finding supports previous research indicating that *VDR* genotype affects rate of bone loss at the proximal femur.[9,16] Others have observed strong associations between the *VDR* alleles and bone density in premenopausal women[10,12,13,39,40] and have postulated

**TABLE 3. Relative Risks* (RR) and 95% Confidence Intervals (CI) for Hip Fracture by Genotype of the Vitamin D Receptor, Stratified by Median Values for Age at Fracture, Body Mass Index, Physical Activity, and Calcium Intake**

| | | *BB vs bb* | | *Bb vs bb* | |
|---|---|---|---|---|---|
| | Cases/Controls† | RR | (95% CI) | RR | (95% CI) |
| Age (years) at fracture | | | | | |
| <66 | 26/52 | 1.20 | (0.33–4.43) | 0.93 | (0.33–2.64) |
| ≥66 | 28/56 | 3.95 | (1.07–14.5) | 0.84 | (0.28–2.54) |
| Body mass index (kg/m$^2$) | | | | | |
| <24.2 | 36/45 | 4.66 | (1.36–16.0) | 2.00 | (0.71–5.61) |
| ≥24.2 | 18/63 | 0.86 | (0.20–3.78) | 0.40 | (0.12–1.35) |
| Physical activity (mets/week)‡ | | | | | |
| <10.2 | 27/53 | 4.73 | (1.19–18.7) | 1.04 | (0.33–3.32) |
| ≥10.2 | 27/54 | 1.31 | (0.36–4.73) | 0.86 | (0.30–2.46) |
| Calcium intake (mg/day)§ | | | | | |
| <1,078 | 20/55 | 4.33 | (0.96–19.5) | 1.63 | (0.47–5.71) |
| ≥1,078 | 30/45 | 1.02 | (0.27–3.89) | 0.67 | (0.24–1.90) |

* Analyses stratified by age at fracture used conditional logistic regression models; analyses stratified by body mass index, physical activity, and calcium intake used unconditional logistic regression models adjusted for age at blood draw.
† Number of cases and controls in analysis.
‡ Measured in units of metabolic equivalents (1 met = the energy expenditure from 1 hour of sitting); the met score was missing for 1 hip control.
§ Calcium intakes were missing for 4 hip cases and 8 hip controls.

that genotype is most influential on development of peak bone mass.

In our exploration of the interactions between genotype and other risk factors for osteoporotic fractures, we found a greater genotype effect in the higher-risk groups with a lower calcium intake, a lower body mass index, or a lower level of physical activity. One would expect that calcium absorption would be compromised if the vitamin D receptor is defective and that this would be most evident at low calcium intakes when active transport with 1,25-dihydroxyvitamin D is crucial for increasing calcium absorption. Indeed, in a metabolic study with 60 postmenopausal women, Dawson-Hughes *et al*[18] found that calcium absorption was lower within the *BB* compared with the *bb* genotype group when the women were on a low-calcium diet and that the increase in fractional calcium absorption was also lower within the *BB* group when they were placed on a high-calcium diet. Calcium absorption was not associated with genotype in subsequent studies among African-American women[25] or men,[28] but it was associated with genotype after correction for dietary calcium and serum 1,25-dihydroxyvitamin D in perimenopausal women.[19] Further evidence that calcium absorption is less efficient among women with the *BB* genotype comes from a calcium supplementation trial among postmenopausal women by Krall *et al*,[16] who observed a greater percentage of bone loss at the femoral neck within the *BB vs* the *bb* genotype among the placebo group but no loss in bone density in any genotype among those receiving the 500-mg-per-day supplement. Also, Salamone *et al*[41] found no association between calcium intake and femoral bone density among premenopausal women with the *bb* genotype, whereas bone density was greater for women with calcium intakes ≥1,036 mg per day compared with those with lower intakes among women with the *BB* or *Bb* genotype.

Our findings that an increased risk of hip fracture was associated with the *BB* genotype only among those with a lower body mass index or a lower level of physical activity need to be corroborated by other investigators. In one study, *VDR* genotype was associated with femoral bone density among nonobese women but not among those who were obese (>30 kg/m$^2$).[27] Regarding physical activity, Salamone *et al*[41] reported a more positive association with femoral bone density among women with the *bb* genotype than among those with the *BB* or *Bb* genotype. Meanwhile, a study among perimenopausal women also found that the association between *VDR* genotype and femoral bone density was modified by physical activity, but the direction was contrary to what we observed; that is, *VDR* genotype was related to bone density among the more active women but not among the less active ones.[42]

In conclusion, we found that the *BB* genotype of the vitamin D receptor was associated with a more than twofold increase in risk of hip fracture among middle-aged and older Caucasian women. The risk was even greater among women who were older when their hip fractured or had a lower-calcium diet, a lower body mass index, or a less active life-style. It is possible that differences between study populations in these or other environmental factors could explain some of the conflicting results from previous studies of *VDR* genotype and femoral bone density.

The *Bsm*I polymorphism may not be the direct cause of lower bone mass or higher rates of fracture but may instead be in close proximity to the responsible locus elsewhere in the *VDR* gene (that is, in linkage disequilibrium). Nevertheless, if these results are confirmed in other studies, *VDR* genotype could be used to identify women at higher risk of hip fracture for pharmacologic, dietary, and other prophylactic interventions.

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