

# Effectiveness of alendronate treatment in postmenopausal women with osteoporosis: relationship with Bsm1 vitamin D receptor genotypes

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## Summary

**OBJECTIVE** To assess whether there is a relationship between the effectiveness of alendronate treatment in postmenopausal women with osteoporosis and Bsm1 vitamin D receptor (VDR) genotypes.

**DESIGN** Prospective baseline-controlled clinical trial. **PATIENTS** Sixty-eight Italian osteoporotic women were enrolled and treated with alendronate at a dose of 10 mg/day for 12 months.

**MEASUREMENTS** At entry and after treatment, lumbar bone mineral density (BMD) and serum osteocalcin (OC) and urinary deoxypyridinoline/creatinine ratio (DPD-Cr) levels were evaluated. DNA was extracted from blood and analysed for the Bsm1 polymorphism of the VDR gene.

**RESULTS** The mean percentage (% ± SD) change from baseline in lumbar BMD was significantly higher ( $P < 0.01$ ) in bb than in BB Bsm1 VDR genotypes ( $7.92 \pm 4.31$  vs.  $3.40 \pm 1.81$ ). No significant difference in lumbar BMD was observed in Bb VDR patients ( $6.01 \pm 3.89$ ) in comparison with other groups. The mean percentage of change in serum OC and urinary DPD-Cr levels was significantly ( $P < 0.01$ ) lower in individuals with bb than in those with BB Bsm1 VDR genotypes ( $-14.34 \pm 2.87$  vs.  $-10.39 \pm 1.43$  and  $-9.61 \pm 5.56$  vs.  $-4.61 \pm 2.31$ ). No significant difference in serum OC and urinary DPD-Cr levels was observed

in Bb VDR patients ( $-12.31 \pm 2.11$  and  $-6.52 \pm 2.65$ ) in comparison with other groups.

**CONCLUSION** The different Bsm1 vitamin D receptor genotypes modify the pharmacological response to alendronate treatment in postmenopausal women with osteoporosis.

Osteoporosis is a multifactorial disease characterized by a low bone mineral density (BMD). Several hormonal and environmental factors affect the risk of osteoporosis, and many genetic factors may strongly influence the sensitivity of the bone to these (Eisman, 1999). In fact, up to 85% of the variance in BMD is genetically determined and various candidate genes have been proposed to be involved in this process (Eisman, 1999). In particular, it has been shown that alleles at the vitamin D receptor (VDR) gene are associated with bone density (Morrison *et al.*, 1994) and that the VDR gene is associated with a particular bone density pattern that varies with chronological age, sex and anatomical site (Gong *et al.*, 1999). The VDR gene polymorphism is also related to a higher prevalence in vertebral fractures (Gomez *et al.*, 1999; Uitterlinden *et al.*, 2001), probably acting independently of BMD (Uitterlinden *et al.*, 2001).

Many therapeutic options are currently available for the prevention and treatment of postmenopausal osteoporosis (Altkorn & Vokes, 2001). Furthermore, few data are available in the literature regarding genetic factors that could influence the clinical response to antiosteoporotic treatments (Keen & Kelly, 1997).

Recent studies suggest that VDR gene polymorphisms may modify the BMD response to calcium (Ca) intake (Dawson-Hughes *et al.*, 1995; Ferrari *et al.*, 1995; Kiel *et al.*, 1997), Ca and vitamin D supplementation (Graafmans *et al.*, 1997; Howard *et al.*, 1995; Wishart *et al.*, 1997), cyclic etidronate administration (Marc *et al.*, 1999) and hormone replacement therapy (HRT) (Deng *et al.*, 1998; Kurabayashi *et al.*, 1999). Thus, VDR gene polymorphisms might be important in predicting the effectiveness of an antiosteoporotic treatment.

Today, administration of alendronate at a standard dose of 10 mg daily is the 'gold standard' for the treatment of postmenopausal osteoporosis (Altkorn & Vokes, 2001), but no data are available in the literature about different BMD responses to this drug and VDR gene polymorphisms.

The aim of the present study was to test whether a relationship exists between a VDR gene polymorphism and the effectiveness

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of alendronate treatment in postmenopausal women with osteoporosis.

## Patients and methods

The procedures used during the study were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The protocol was approved by the local ethics committee of the University of Naples.

Before entering the study, the purpose of the protocol was explained to all women attending the Departments of Gynaecology of the Universities of Catanzaro and Naples. Written informed consent was obtained by all subjects.

### Patients

Between January and August 2000, 68 ambulatory postmenopausal women (FSH > 40 IU/l, 17 $\beta$ -oestradiol (E2) < 20 pmol/l) with osteoporosis were enrolled in the study protocol.

Inclusion criteria were: natural postmenopause, and BMD values of at least 2.5 standard deviations (SD) below the mean bone density of the peak value for sex-matched healthy young adults ( $-2.5$  T-score) at posterior–anterior lumbar spine. All women enrolled were genetically unrelated.

Exclusion criteria were: active rheumatoid arthritis; gastrointestinal or liver disease; metabolic, neoplastic or endocrine diseases; history of acute or recurrent vascular thrombosis; secondary causes of osteoporosis, such as hyperparathyroidism, Paget's disease of bone, or renal osteodystrophy; previous treatment with bisphosphonates, sodium fluoride, calcitonin, oestrogen, anabolic steroids, corticosteroids, Ca, vitamin D, or phosphate (P); treatment with corticosteroids, thiazide diuretics or other drugs interfering with bone metabolism; serum creatinine (Cr) > 133  $\mu$ mol/l, history of gastrointestinal side-effects; body mass index (BMI) < 18 kg/m<sup>2</sup> or > 30 kg/m<sup>2</sup>. Women with plasma 25-OH-vitamin D levels lower than 25 nmol/l or abnormal serum Ca (normal values 2.2–2.6 mmol/l), P (normal values 1.0–1.4 mmol/l) and PTH (normal values 10–65 ng/l) concentrations were excluded from the study.

Also excluded were women who regularly used any medication that had the potential to cause gastrointestinal irritation, or who used drugs to inhibit gastric acid secretion, women who smoked more than 20 cigarettes per day, or who drank more than three alcoholic beverages per day.

### Treatment and study protocol

All subjects received alendronate (Fosamax, Merck Sharp & Dhome, Rome, Italy) at a dose of 10 mg/day. Patients were instructed to take the medication orally in the morning at least 30 min before breakfast with abundant water and on an empty stomach after

an overnight fast, and to remain upright for at least 30 min after dosing. The duration of the treatment was 12 months.

At baseline and after treatment, BMD and bone metabolism were measured in all groups as detailed below. Both patients and clinicians were blind with respect to these results throughout the study period.

At baseline and every 3 months of treatment, Ca intake, alcohol consumption and physical activity were evaluated as described previously (Palomba *et al.*, 1999, 2002). Ca intake and alcohol consumption were assessed by a dietary history of patients using a semiquantitative diet questionnaire developed by dieticians of the University of Naples. Ca intake was expressed as a score ranging from 1 to 3, according to the following scale: score 1 for a Ca intake < 500 mg/day, score 2 for a Ca intake of 500–1000 mg/day, and score 3 for a Ca intake > 1000 mg/day. Alcohol consumption was also expressed as a score ranging from 1 to 3, according to the following scale: score 1 for an alcohol consumption of < 1000 mg/day, score 2 for an alcohol consumption of 1000–2000 mg/day, and score 3 for an alcohol consumption of > 2000 mg/day. A semiquantitative questionnaire was also used to evaluate the patients' daily physical activity. Physical activity was expressed as a score ranging from 1 to 3, according to the following scale: score 3 (high physical activity) was assigned to women who exercised regularly; score 2 (moderate physical activity) was assigned to women who did not exercise regularly but participated daily in activities such as cleaning the house, climbing stairs, or walking to work, to the bus stop, or to a restaurant; score 1 (low physical activity) was assigned to women who did not participate in any of above-mentioned activities.

No dietary restrictions or changes were implemented during the study. To ensure adequate Ca intake, all patients with a Ca intake of less than 1000 mg received daily supplements of elemental Ca in the form of an effervescent tablet composed of Ca carbonate (500 mg/day; Cacit, Procter & Gamble, Rome, Italy) to achieve a total daily Ca intake of at least 1000 mg. This supplement was taken at lunch.

### BMD measurement

The BMD was determined by dual energy X-ray absorptiometry (Hologic QDR 1000, Waltham, MA, USA) at posterior–anterior lumbar spine (vertebrae L2 to L4).

The precision of the measurements expressed as coefficient of variation (CV) *in vitro* for repeated BMD determinations for two standard phantom in our laboratory was 0.41% and 0.43% for the Universities of Naples and Catanzaro, respectively. The CV *in vivo* was evaluated comparing two measurements performed at 7-day intervals in 40 volunteers and was 1.0% and 1.2% for the Universities of Naples and Catanzaro, respectively.

The absorptiometries were examined by the same observer blind with respect to different VDR genotypes.

We used the mean of three scans to calculate bone mineral content (BMC). The BMD values were calculated by the software of the bone densitometer dividing the BMC (g/cm) for the bone width (cm) and expressed directly as an index (g/cm<sup>2</sup>).

Vertebral fractures were assessed from thoracic and lumbar (T4–L4) lateral and anterior–posterior spinal radiographs taken at baseline and from lateral spinal radiographs taken at the end of the study. Potential fractures were identified by quantitative morphometry according to the guidelines of the US National Osteoporotic Foundation Working Group on Vertebral Fractures (Kiel, 1995), and subsequent visual verification of incident fractures was performed by a qualified radiologist.

### Biochemical assays

At entry serum FSH and E<sub>2</sub> levels were assayed in all women to confirm the postmenopausal status. At entry and after treatment, Ca, P, PTH, osteocalcin (OC) and urinary creatinine (Cr) and deoxypyridinoline (DPD) levels were determined using commercial kits (Palomba *et al.*, 2002).

In particular, serum OC levels and urinary Cr-corrected free DPD were used as markers of bone formation and of bone resorption, respectively. Serum OC levels (reference range 0.53–2.34 nmol/l) were assayed by an immunoradiometric assay (IRMA) (Diagnostic Products Corporation, Los Angeles, CA, USA) with a sensitivity of 0.02 nmol/l, and intra- and interassay CVs of 4.5% and 3.5%, respectively. Urinary DPD concentrations (reference range normalized for Cr levels 3.0–7.4 nmol/mmol) were assayed by an enzyme immunoassay (EIA) (Metra Biosystems, Milan, Italy) with a sensitivity of 1.1 nmol/l, and intra- and interassay CVs of 7.6% and 5.5%, respectively. Urinary concentrations of Cr (reference range 8.8–14.1 mmol/24 h) were measured with the use of an autoanalyser (Monarch 1000, Instrumentation Laboratory, Milan, Italy). Cr-corrected values were calculated by dividing DPD by urinary Cr measured using a standard colorimetric assay (DPD-Cr).

Blood and 24-h urine samples were collected after an overnight fast between 0830 and 0930 h to avoid the interference of circadian changes. The urine samples were taken using tubes covered with light-resistant paper. Patients were asked to refrain from eating foods containing fat or gelatine within 12 h of their clinic visit. Serum samples were separated within 1 h from collection and kept frozen at –80 °C, and urine was stored at –20 °C until biochemical analysis. All samples from the same woman were analysed in the same assay and were analysed blind by a central laboratory (University of Catanzaro).

### DNA analysis

The DNA analysis was performed in the Department of Clinical and Experimental Medicine of the University of Naples.

At entry, DNA was extracted from whole-blood samples with the salting-out procedure described by Miller *et al.* (1988). Genotypic analysis of VDR gene polymorphisms was determined by polymerase chain reaction (PCR) amplification and enzymatic digestion of the products with BsmI restriction enzyme. The forward and reverse primers were modified from Sainz *et al.* (1997).

PCR was performed with a Techne Progene Thermal Cycler (Cambridge, UK) under standard conditions for 30 cycles and at 65 °C annealing temperature.

DNA was digested with BsmI under standard conditions and the products were analysed by electrophoresis on a 1.5% agarose gel containing ethidium bromide.

The alleles were defined as ‘B’ or ‘b’ in the absence or in the presence of the restriction site, respectively.

### Safety evaluation

Standard clinical evaluations and laboratory analyses, including haematological, renal function and liver function tests, and microscopical examinations of sediment from midstream urine specimens were performed before treatment and after every 6 months. A mammography was performed before treatment and then yearly.

The subjects were instructed to report the appearance of adverse experiences (AEs) in a daily diary.

### Statistical analysis

The analysis of variance (ANOVA) followed by the Newman–Keuls multiple range test was used to compare multiple measures of age, time since menopause, body mass index (BMI), BMD and biochemical data. Wilcoxon’s signed rank-test was used to compare parity, cigarettes smoked, alcohol consumption, Ca intake and physical activity. The proportion of women receiving Ca supplements in the three groups of polymorphism was compared using the  $\chi^2$ -test. Fisher’s exact test was used to compare the incidence of AEs between treatment groups. The statistical analysis was performed using SPSS 9.0 (SPSS Inc., Chicago, IL, USA).

The statistical significance was set at  $P < 0.01$ . Data were normally distributed and were expressed as mean  $\pm$  SD.

### Results

Sixty-four of 68 enrolled osteoporotic postmenopausal women were analysed.

No drop-out was due to drug-related AEs. Three women (one from each VDR genotype group) dropped out from the study because they stopped treatment during the third month of the alendronate period for personal reasons. In addition, one other woman (in the bb VDR group) dropped out because she experienced an AE consisting of surgical intervention for gall stones.

	VDR genotypes		
	BB	Bb	bb
No. (%)	12 (18.75)	23 (35.93)	29 (45.31)
Age (years)	64.33 ± 4.42	65.39 ± 3.33	64.59 ± 6.90
BMI (kg/m <sup>2</sup> )	25.16 ± 1.65	25.59 ± 1.31	25.26 ± 2.02
Time since menopause (years)	14.42 ± 4.17	14.91 ± 3.68	14.34 ± 2.88
FSH (IU/l)	62.9 ± 13.4	68.0 ± 11.7	65.3 ± 11.9
E <sub>2</sub> (pmol/l)	17.2 ± 1.9	16.1 ± 1.7	17.4 ± 1.3
Parity (number)	2.0 ± 0.4	2.1 ± 0.4	1.8 ± 0.3
Smoking history			
Never smoked (%)	6 (50.0)	13 (56.5)	15 (51.7)
Past smoker (%)	2 (16.7)	4 (17.4)	5 (17.2)
Current smoker (%)	4 (33.3)	6 (26.1)	9 (31.1)
Cigarettes smoked (number/day)	5.2 ± 3.1	5.6 ± 3.8	4.7 ± 3.5
25-OH-vitamin D (nmol/l)	65.1 ± 13.9	72.2 ± 15.1	69.7 ± 14.6
Ca (mmol/l)	2.44 ± 0.19	2.42 ± 0.13	2.39 ± 0.16
P (mmol/l)	1.21 ± 0.22	1.14 ± 0.15	1.19 ± 0.18
PTH (ng/l)	45.6 ± 13.5	43.9 ± 11.1	46.2 ± 15.7
Ca intake score*	1.8 ± 0.8	1.7 ± 0.8	1.7 ± 0.8
Women taking Ca supplementation (%)	9 (75.0)	18 (78.3)	23 (79.3)
Alcohol intake score†	1.2 ± 0.5	1.3 ± 0.6	1.4 ± 0.5
Physical activity score‡	1.3 ± 0.7	1.3 ± 0.6	1.4 ± 0.7
Lumbar spine T-score	-3.33 ± 0.60	-3.35 ± 0.81	-3.47 ± 1.14

Values are expressed as mean ± standard deviation (SD); BMI, body mass index; E<sub>2</sub>, oestradiol.

\*1 = < 500 mg/day, 2 = 500–1000 mg/day, 3 = > 1000 mg/day; †1 = < 1000 mg/day, 2 = 1000–2000 mg/day, 3 = > 2000 mg/day; ‡1 = low, 2 = moderate, 3 = high.

After alendronate treatment, we observed a significant ( $P < 0.01$ ) increase in lumbar spine BMD ( $0.577 \pm 0.074$  vs.  $0.613 \pm 0.079$  mg/cm<sup>2</sup>, before and after treatment, respectively) in our sample studied. The change in BMD (mean ± SD) from baseline was  $6.39 \pm 4.12\%$ . Serum OC ( $1.12 \pm 0.03$  nmol/l) and urinary DPD-Cr levels ( $6.11 \pm 0.12$  nmol/mmol) were significantly ( $P < 0.01$ ) lower in comparison to basal values ( $1.18 \pm 0.03$  and  $6.54 \pm 0.14$  for OC and DPD-Cr, respectively). The changes in serum OC and urinary DPD-Cr levels (mean ± SD) from baseline were  $12.7 \pm 1.1\%$  and  $7.6 \pm 0.9\%$ , respectively.

The VDR genotype prevalence in the study population is shown in Table 1. In our population study, the BsmI VDR genotype frequencies were in Hardy–Weinberg equilibrium (Ott, 1999). Considering the different BsmI VDR genotypes, no significant differences in baseline data were detected between the three groups of women (Table 1).

At entry, there was also no significant difference between VDR genotype groups with respect to lumbar BMD, and serum OC and urinary DPD-Cr levels (Table 2). After alendronate treatment, a significant ( $P < 0.01$ ) difference in lumbar BMD, and in serum OC and urinary DPD-Cr levels was observed in each group of VDR genotype in comparison with baseline values.

**Table 1** Baseline characteristics of the subjects according to the VDR gene BsmI polymorphism

Furthermore, no statistically significant difference was detected between the three groups of BsmI VDR genotypes (Table 2).

The mean percentage change (% ± SD) of lumbar BMD was significantly higher in patients homozygous for bb in comparison with those homozygous for BB genotypes ( $7.92 \pm 4.31$  vs.  $3.40 \pm 1.81$ ;  $P < 0.01$ ). No significant difference in lumbar BMD change ( $6.01 \pm 3.89$ ) was observed in patients heterozygous for Bb in comparison with those homozygous for BB and bb.

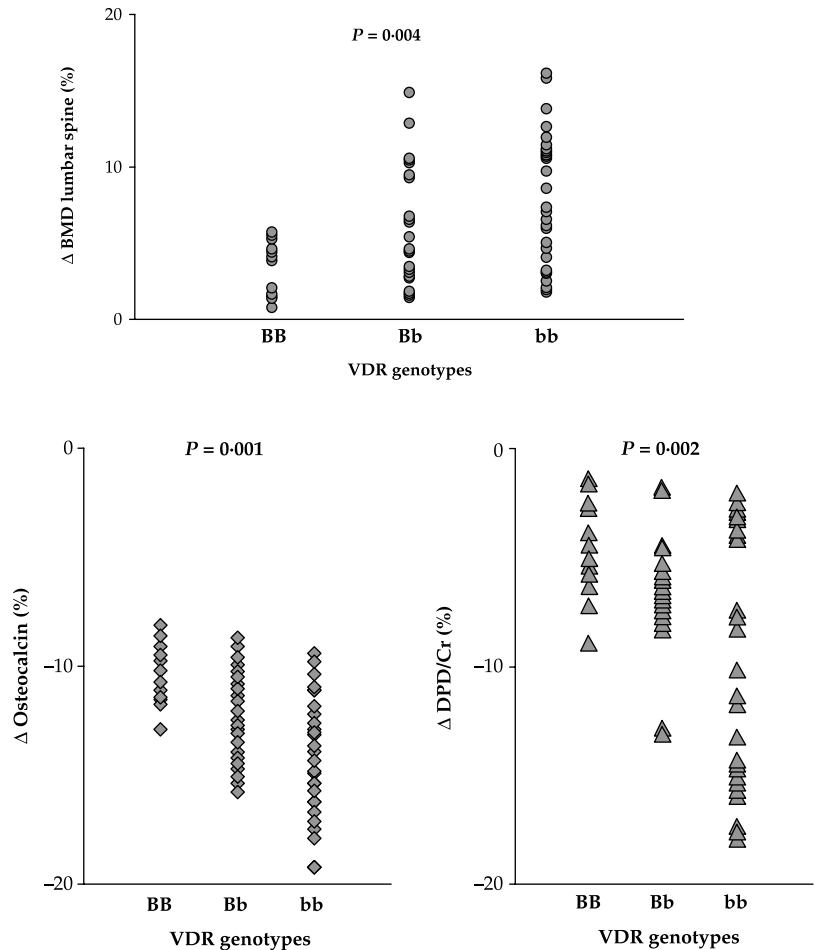
The mean percentage change in serum OC levels was significantly lower in patients with bb compared to those with BB genotypes ( $-14.34 \pm 2.87$  vs.  $-10.39 \pm 1.43$ ;  $P < 0.01$ ), whereas no significant difference was observed in those heterozygous for Bb VDR patients ( $-12.31 \pm 2.11$ ) in comparison with other homozygous groups. The mean percentage change in urinary DPD-Cr levels was significantly lower in those homozygous for bb than in those homozygous for BB BsmI VDR genotypes ( $-9.61 \pm 5.56$  vs.  $-4.61 \pm 2.31$ ;  $P < 0.01$ ) whereas no significant difference was observed in patients heterozygous for Bb VDR genotypes ( $-6.52 \pm 2.65$ ) in comparison with other homozygous groups.

Figure 1 shows the individual percentage change in lumbar BMD and in serum OC and urinary DPD-Cr levels in each woman according to BsmI VDR genotypes after 12 months of alendronate administration.

**Table 2** Bone mineral density (BMD) and biochemical markers before and after 12 months of alendronate treatment (10 mg/day) according to the VDR gene BsmI polymorphism

	VDR genotypes		
	BB	Bb	bb
<b>BMD lumbar spine (g/cm<sup>2</sup>)</b>			
Baseline	0.582 ± 0.081	0.579 ± 0.077	0.573 ± 0.071
After treatment	0.602 ± 0.085*	0.613 ± 0.081*	0.618 ± 0.076*
<b>Osteocalcin (nmol/l)</b>			
Baseline	1.18 ± 0.10	1.17 ± 0.12	1.18 ± 0.12
After treatment	1.05 ± 0.09*	1.03 ± 0.10*	1.01 ± 0.12*
<b>DPD/Cr ratio (nmol/mmol)</b>			
Baseline	6.71 ± 0.46	6.68 ± 0.55	6.64 ± 0.59
After treatment	6.40 ± 0.53*	6.23 ± 0.53*	6.01 ± 0.66*

Values are expressed as mean ± standard deviation (SD); DPD/Cr, deoxypyridinoline/creatinine ratio; \**P* < 0.01 vs. baseline.



**Fig. 1** Percentage change in lumbar BMD and in serum OC and urinary DPD-Cr levels in each patient classified according to the BsmI VDR genotypes. A significant difference (*P* = 0.004, *P* = 0.001 and *P* = 0.002 for lumbar BMD, serum OC and urinary DPD-Cr levels, respectively) was observed between patients homozygous for bb and those homozygous for BB BsmI VDR genotypes.

**Discussion**

Alendronate is a potent and specific inhibitor of osteoclast-mediated bone resorption. Its administration prevents postmenopausal

bone loss in women without osteoporosis and it is an effective treatment for osteoporotic women. A significant reduction in the incidence of vertebral and nonvertebral fractures in postmenopausal osteoporotic women with or without pre-existing fractures

has been demonstrated with the use of alendronate (Jeal *et al.*, 1997; Altkorn & Vokes, 2001; Sharpe *et al.*, 2001).

Prolonged and continuous treatment with alendronate at low doses has also been shown to be effective in preventing postmenopausal and glucocorticoid-induced bone loss (Sharpe *et al.*, 2001). Indeed, in postmenopausal osteoporotic women the addition of 5 mg alendronate to HRT induced a greater increase in BMD than HRT alone but not significantly different in comparison with the addition of a standard dose of 10 mg daily (Palomba *et al.*, 2002).

According to previous studies, our results confirm that 12 months of continuous oral alendronate 10 mg/day induces a significant increase in BMD lumbar spine in postmenopausal women with osteoporosis (Jeal *et al.*, 1997; Sharpe *et al.*, 2001; Palomba *et al.*, 2002). Furthermore, the aim of our study was to test the association between the alendronate-induced bone gain with VDR genotypes. Indeed, the lumbar spine increases in BMD are significantly greater in women homozygous for bb compared to those homozygous for BB. Serum and urinary levels of bone turnover markers also decreased significantly more in bb than in BB subjects. Heterozygous Bb VDR patients showed an intermediate percentage change in lumbar BMD, serum OC and urinary DPD-Cr levels that was not significantly different from that seen in those homozygous for BB and bb.

In our study, the BsmI VDR genotypes frequencies were in Hardy–Weinberg equilibrium (Ott, 1999) and the BsmI VDR allelic frequencies in the study population were comparable to published data in European postmenopausal and osteoporotic unrelated women (Vandevyver *et al.*, 1997).

Our data are a further confirmation that bone metabolism is largely controlled by genetic mechanisms, and that bone loss and gain are also genetically determined with respect to antiosteoporotic treatments. In particular, the significant difference in lumbar spine BMD change observed, after treatment, between homozygous bb and BB VDR subjects supports the initial hypothesis that different BsmI VDR genotypes modify the pharmacological response to alendronate treatment in osteoporotic women.

To obtain results with minimal confounding factors we enrolled women with no significant differences in demographic characteristics, and with a similar Ca dietary intake of at least 1000 mg daily and with serum 25-OH-vitamin D levels higher than 25 nmol/l (Dawson-Hughes *et al.*, 1995; Ferrari *et al.*, 1995; Graafmans *et al.*, 1997; Howard *et al.*, 1995).

At present, there is no explanation of the relationship between alendronate action and VDR polymorphisms, and the mechanism by which the different VDR genotypes may account for changes in the bone gain after alendronate administration is unknown. It has been demonstrated that alendronate impairs bone resorption induced by  $1,25(\text{OH})_2\text{D}_3$  and retinoids, and that it inhibits the  $1,25(\text{OH})_2\text{D}_3$ /VDR-induced production of osteocalcin (Fleisch, 1998; Rogers *et al.*, 2000).

In a recent paper (Kurabayashi *et al.*, 1999), the VDR and oestrogen receptor gene polymorphisms were related to the effectiveness of HRT on bone density in Japanese women. In this retrospective study (Kurabayashi *et al.*, 1999), it was shown that subjects with genotype bb (TT in Japanese women) exhibit a significantly greater increase in BMD than those with Bb genotype after 2 years of HRT. Furthermore, only one woman was homozygous BB and was not included in the results. Indeed, the population studied was very heterogeneous and unselected with regard to dietary, BMD and progestin balance.

Our results are partially in contrast with those published by Marc *et al.* (1999). In that study, a higher response to etidronate treatment was observed in BB in comparison with bb VDR genotypes (Marc *et al.*, 1999). There are various possible reasons to explain this discrepancy in the results. First, the Ca supplementation was administered to each woman without a clear evaluation of the daily Ca intake. In addition, no selection was performed according to the plasma vitamin D levels. Furthermore, we cannot exclude the different pharmacological properties between alendronate and etidronate (Russel & Rogers, 1999).

In conclusion, our study demonstrates that a vitamin D receptor gene polymorphism plays a role in the pharmacological response to alendronate treatment and confirms that knowledge of the genetic background could improve the selection of optimal antiosteoporotic treatment. Further studies are necessary to clarify the possible role of the allelic variants of the vitamin D receptor and of other genes in the modulation of the pharmacological response to antiosteoporotic treatment.

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