

NOTE

Vitamin D Receptor Genotype Is Associated with Cortical Bone Loss in Japanese Patients with Primary Hyperparathyroidism

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Abstract. Vitamin D receptor (VDR) genotype was determined in 66 Japanese patients with primary hyperparathyroidism (pHPT). In contrast to previous report showing an association between VDR genotype bb and the development of pHPT in a Swedish population, we did not find any differences in the frequencies of the VDR genotypes between pHPT and the control. The bone mineral density in the radius was significantly lower (Z score, -1.723 ± 1.819) in bb genotype than in BB/Bb genotype ($+0.255 \pm 2.344$) in pHPT patients. Based on the fact that PTH requires vitamin D₃ to take effect on calcium mobilization from bone, it is possible that VDR polymorphism may influence the PTH action on bone.

Key words: Primary hyperparathyroidism, Vitamin D receptor, Polymorphism, Bone mineral density
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CARLING *et al.* reported an association between the vitamin D receptor (VDR) genotype bb and the development of primary hyperparathyroidism (pHPT) in a Swedish population [1]. Although they found no difference in bone mineral density (BMD) among pHPT patients having the three genotypes (BB, Bb, bb), it is still possible that the VDR genotype is associated with the degree of bone loss. Because their pHPT patients were recruited from a health screening and because no difference was found between pHPT patients and age-matched controls in BMD, the severity of the disease was probably mild. In this study, we examined whether the VDR genotype is associated with the development and severity of both pHPT and BMD in Japanese patients.

Subjects and Methods

We analyzed 66 Japanese patients (14 males and 52 females, mean age at diagnosis 56 ± 12 years) and 71 age-matched controls (8 males and 63 females, mean age 62 ± 8 years). All subjects agreed to participate in this study and gave the informed consent. The pHPT patients were diagnosed by histological examination as well as biochemical and radiographic examination during the hospitalization at Kobe University Hospital. Cases with multiple endocrine neoplasm, familial hypocalciuric hypercalcemia or indistinguishable from tertiary hyperparathyroidism were excluded from the analysis. BMD was measured at the lumbar spine (L2-L4) and at the one-third distal site of the radius by dual energy X-ray absorptiometry and by single photon absorptiometry, respectively. Biochemical and BMD data used were obtained as soon as possible after the discovery of the diseases. The VDR genotype was determined from the peripheral

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leukocyte DNA as previously described [1]. The presence and absence of the Bsm I restriction site were indicated by b and B, respectively. Statistical analysis was performed by ANOVA.

Results

The mean standard deviations from average BMD at each age (Z-score) of the controls were -0.001 ± 1.048 at the lumbar spine and 0.035 ± 1.140 at the radius. No difference was found in the frequencies of the B or b alleles between pHPT patients and the controls (Table 1). Because of the low frequency of the B allele, we divided the subjects into two groups according to the presence or absence of the B allele, that is the BB/Bb group and the bb group. There were no differences between the two groups of pHPT patients in serum levels of calcium, phosphorus or PTH, or in weight of the parathyroid gland (data not shown). But, the radial BMD of pHPT patients before treatment was significantly lower in the bb group than in the BB/Bb group, although the difference was not significant in the lumbar BMD (Table 1).

Discussion

VDR genotype in primary [3] and secondary [4] hyperparathyroidism was analyzed in Japanese patients as well. Our data on the VDR genotype frequency in pHPT were consistent with the results of Nagasaka *et al.* [2], in which the number of patients [22] was too small to reach a firm conclusion. The overall frequencies of the B and b alleles were mostly consistent with those previously

reported in an Asian population [5–7]. The radial bone loss in bb in pHPT was opposite to the results of previous reports on healthy Japanese subjects [6, 7]. This tendency was the same even when only female patients were analyzed (data not shown). Since the cortical bone (radial BMD) is more likely to be affected and the trabecular bone (lumbar BMD) is preserved in pHPT [8], the radial bone loss in the present study group is considered to be caused by excessive PTH. The interaction between vitamin D₃ and PTH plays a crucial role in maintaining systemic calcium homeostasis, and it is well known that PTH requires vitamin D₃ to take effect on calcium mobilization from bone [9, 10]. The associations between the vitamin D₃ effects and VDR genotypes were reported concerning the intestinal calcium absorption [11] and the bone metabolic markers [12]. Taken together, it is considered that the presumed difference in the vitamin D₃ effect based on the VDR gene polymorphism might alter the PTH action on bone, that is, calcium-mobilizing action of PTH on bone might be stronger, resulting in severer bone loss in bb group, compared to BB/Bb group. The present findings also suggest that varied VDR expression due to allelic polymorphism of VDR gene might influence bone mass and clinical characteristic of pHPT. We cannot clearly explain the reason why the present findings from pHPT patients were opposite to the previous evidence from healthy subjects that BMD was significantly higher in the bb group [2, 6, 7]. But it is interesting to speculate that a difference might exist in the modification of the PTH action on cortical bone by VDR polymorphism between the conditions of endogenous PTH excess and physiological PTH level. In conclusion, our results indicate that the

Table 1. VDR genotype and its association with bone mineral density (BMD) in pHPT

	pHPT			Control		
	BB	Bb	bb	BB	Bb	bb
VDR genotype (%)	4.5	19.7	75.8	5.6	14.1	80.3
Lumbar BMD (Z-score)	-0.119 ± 0.809 (n=9)	-0.837 ± 1.658 (n=24)		-0.055 ± 1.010 (n=14)	$+0.012 \pm 1.066$ (n=57)	
Radial BMD (Z-score)	$+0.255 \pm 2.344^*$ (n=8)	-1.723 ± 1.819 (n=26)		-0.212 ± 1.147 (n=14)	$+0.096 \pm 1.14$ (n=57)	

Means \pm SD shown. * $P < 0.05$ vs. bb.

VDR genotype does not influence the development of pHPT in Japanese patients, but the VDR genotype bb in pHPT patients should be considered a risk factor for severe bone loss.

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