Potential role of vitamin D receptor gene polymorphism in determining bone phenotype in young male athletes

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The vitamin D receptor (VDR) gene has been targeted in the research on the genetic determinant influencing bone status (15, 29) because it regulates bone homeostasis through the vitamin D-endocrine system (19, 21). Whether the bone of individuals with a particular genotype is more sensitive to exercise intervention than that of other genotypes has also been examined (24, 47, 48). Furthermore, whereas some epidemiological studies suggest that individual bone mineral density (BMD) is determined by the interaction between the physical activity level and the VDR variations in its 3′-untranslated regions (4, 35, 38), another study did not find a similar genetic effect of the VDR (14).

Another polymorphism resulting from a C-to-T transition within exon 2 of the VDR gene, defined by endonuclease Fok I (“F” for the absence of the restriction site and “f” for its presence), creates an upstream initiation codon and leads to the production of VDR proteins that differ in length by three amino acids (2, 16, 37). Significant association of the FF genotype with greater BMD has been reported in healthy populations (1, 2, 16, 20, 25, 26). These observations provide a hypothesis that the shorter F allele may function at increased efficiency in maintaining bone homeostasis, although analyses of its function on the cellular level have not reached unequivocal agreement (2, 10, 17, 23, 50).

Tajima et al. (47) revealed differences in the responses of bone metabolism to strenuous resistance exercise training in young Japanese men with different genotypes of the VDR detected by Fok I. In their subsequent study, Nakamura et al. (30) reported that BMD in young male athletes with different impact loading depended on the VDR genotypes, implying a new notion that the FF genotype may respond more sensitively to differences in impact loading in regulating BMD, rather than merely being a predictor of high bone mineral density (BMD) is determined by the interac-

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THE VDR Genotypes, as detected by endonuclease site, in the adaptations of bone to long-term impact loading: polymorphism, which locates at the translation initiation site, is to evaluate the role of the vitamin D receptor (VDR) gene in determining bone phenotype in young male athletes.

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THERE IS A GROWING REALIZATION that the physical response to a particular environmental stimulus, such as exercise, may be mediated by individual genetic variability (7). In 2001, the first version of the human gene map for health-related fitness phenotypes was published (34). These facts necessitate the inclusion of gene-environment interaction in physiological studies, particularly those in applied physiology, if we are to understand the intricate processes that determine human phenotypes through exercise (7).

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BMD. These findings suggested the hypothesis that the adaptive response of bone to exercise may depend in some part on the interindividual allelic variance of the VDR gene at the translation initiation site (30, 47).

BMD is a surrogate of the breaking strength of bone in vitro (46), and its measurement is frequently used to estimate the quantitative phenotype of bone in an individual. Dual-energy X-ray absorptiometry assesses BMD as the mass of bone mineral content (BMC) per unit of projected area. In children, the three-dimensional shape and size of bones change dramatically throughout growth (31), and the increase in BMD during puberty is primarily due to an expansion in bone size (39, 42, 43). Thus a simple adjustment of BMC based on projected area may be inadequate to describe the true characteristics in growing bone (31). Additionally, mechanical loading markedly alters the size and shape of the skeleton via the mechanotransduction system (49). The adaptation in BMD among young athletes may result from potential alterations in bone geometrical characteristics (3, 18, 22), although most studies of the effects of vigorous exercise on bone structure have been almost exclusively restricted to BMD (9, 11, 28, 33, 45). In fact, lifetime physical activity seemed to have more influence on bone mass, area, and width than on density, at least in men (6).

The purpose of this cross-sectional study was to evaluate the role of the genetic influence in the adaptations of bone phenotypes to long-term impact loading. For this aim, we assessed not only BMD but also bone volume and BMC in highly trained young male athletes and age-matched controls in relation to polymorphism in the VDR gene. The VDR genotypes were distinguished by the position of the translation initiation codon detected by the endonuclease Fok I.

MATERIALS AND METHODS

Subjects. Eighty-eight healthy young Japanese male volunteers, including 44 competitive athletes and 44 controls, were recruited from the University of Tsukuba. At the time of the study, the athletes were engaged in weight-bearing sports with a high-impact load on their lower limbs (volleyball, basketball, handball, and track-and-field events such as the high jump and triple jump) and had intensively trained for >6 yr. The control group consisted of 44 nonathletic men who did not engage in regular exercise or sports. All participants had no history of metabolic bone disease or use of a pharmaceutical agent that could affect bone turnover. Written, informed consent was obtained from each participant before the study, and the project was approved by the University of Tsukuba Human Subjects Institutional Review Board.

Analysis of VDR genotype. Blood samples were collected in EDTA tubes, and DNA was extracted from whole blood by using the sodium iodide method (DNA extractor WB kit, Wako Pure Chemical Industries, Osaka, Japan). The VDR genotyping was determined by PCR as described (2, 16), with slight modifications, followed by restriction fragment length polymorphism analysis using the endonuclease Fok I, which recognizes ATG as part of its restriction site. To amplify the region of the VDR gene, including the translation initiation site in exon 2, PCR was performed with the use of modified primers (forward: 5’-AGATGCCACCCCTTGGCTGA-3’ and reverse: 5’-ATGGAAACACCTTGCTTCTTCCCTC-3’). The PCR products were digested with Fok I endonuclease (Takara Shuzou, Otsu, Japan) at 37°C for 2 h and then electrophoresed through a 2% agarose gel containing ethidium bromide. The presence and absence of the Fok I site were denoted as f and F, respectively, and individuals were categorized as ff or FF homozygotes and Ff heterozygotes (16).

<table>
<thead>
<tr>
<th>Table 1. Physical characteristics of the subjects</th>
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<tr>
<td><strong>Control</strong> (n = 44)</td>
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<tr>
<td>Exercise career, yr</td>
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<tr>
<td>Age, yr</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<tr>
<td>Body fat, %</td>
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<tr>
<td>Lean mass, kg</td>
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<tr>
<td>BMC, g</td>
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</table>

Values are means ± SD. BMC, bone mineral content. *Statistically significant difference from control group (P < 0.01).

The height and width of the body of the third lumbar (L3) vertebra were determined from a posteroanterior scan of the lumbar spine. The volume of L3 was calculated as scanned area2.5% (8). The femoral neck volume was approximated as length × width2 × scanning height, where width = scanned area/scanning length (27). The mean value of both sides of the femoral neck was accepted as the index of the femoral neck.

Data analysis. Values described in this study are presented as means ± SD. To adjust potentially confounding differences related to height or weight, a stepwise multivariate linear regression analysis was performed to determine predictors for each index. The adjusted values were also expressed as a z score (i.e., as a number of standard deviations from the genotype-matched control mean value). Group differences in descriptive data were evaluated by using an unpaired Student’s t-test, and the interaction between the VDR genotypes and impact loading activity was assessed by multifactor ANOVA with Fisher’s post hoc test. Statistical significance was established at P < 0.05.

RESULTS

Physical characteristics of the athletes. The athletes in the present study had started their regular exercise training before the growth spurt of adolescence, and, on average, they were involved in sports at a competitive level for 8 yr through adolescence and currently training at least 5 days per week. Characteristics of the study groups are shown in Table 1. The athletic group was taller and heavier than the control group. Additionally, the athletes had greater lean mass and BMC than the controls.

The confounding factors related to body size were assessed by a stepwise multivariate linear regression analysis for each index of bone phenotype, and then data are represented as the adjusted values by height and/or weight. When the adjusted values of the lumbar spine and femoral neck were compared between the
Table 2. Adjusted BMD, BMC, and bone volume at lumbar spine and femoral neck

<table>
<thead>
<tr>
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<th>Control</th>
<th>Athlete</th>
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<tbody>
<tr>
<td>Lumbar spine</td>
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<tr>
<td>BMD, g/cm²</td>
<td>1.027 ± 0.098</td>
<td>1.199 ± 0.117*</td>
</tr>
<tr>
<td>BMC, g</td>
<td>17.5 ± 2.3</td>
<td>21.6 ± 2.7*</td>
</tr>
<tr>
<td>Volume, cm³</td>
<td>68.5 ± 7.0</td>
<td>74.7 ± 8.7*</td>
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<tr>
<td>Femoral neck</td>
<td></td>
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<tr>
<td>BMD, g/cm²</td>
<td>0.993 ± 0.121</td>
<td>1.209 ± 0.106*</td>
</tr>
<tr>
<td>BMC, g</td>
<td>5.1 ± 0.6</td>
<td>6.5 ± 0.7*</td>
</tr>
<tr>
<td>Volume, cm³</td>
<td>13.6 ± 2.2</td>
<td>15.9 ± 2.1*</td>
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Values are means ± SD. BMD, bone mineral density. *Statistically significant difference from control group (P < 0.01).

The athletes and controls, the athletes had significantly greater volumes and BMC than the controls in both sites (Table 2).

Prevalence of the VDR genotype and characteristics of the subjects. Analysis of restriction fragment length polymorphism by Fok I of all 88 subjects in this study revealed that 37 (42.0%) were genotype FF, 2 (2.3%) were ff, and 49 (55.7%) were Ff. Because of the low frequency of the ff genotype, influences of the genetic factor on bone phenotypes were estimated between the FF and the Ff. There were no differences in the exercise careers and physical characteristics between the genotypes of both groups (Table 3), and a similar prevalence in the sport(s) participated in was seen in the two athletic groups based on their VDR genotypes.

Influences of VDR genotype on bone phenotypes. In the control group, there were no differences in bone phenotypes between the VDR genotypes (Table 4). However, at the lumbar spine, the athletes with the FF genotype had not only 7.7% greater BMC but also 7.8% greater volume than those with the Ff (Table 4). Moreover, significant interactions between the VDR polymorphism and impact loading activity on the BMC and bone volume were found. However, there was no difference in the BMD at lumbar spine according to VDR genotypes among the athletes (Table 4).

No statistically significant differences in the phenotypes of the femoral neck between the genotypes were observed in the athletes (Table 4).

Comparison of bone phenotypes between controls and athletes in each VDR genotype. Compared with the control values in each genotype after transformation to the z scores, the bone volume of the lumbar spine in the athletes was enlarged in the FF (1.63 ± 1.44; P < 0.01) but not in the Ff genotype (0.36 ± 0.99; P = 0.21) (Fig. 1). The BMC and BMD of the athletes were significantly greater than those of the controls in both genotypes, whereas the augmentation of the spinal BMC, evaluated by the z score, was more notable in the athletes with the FF (2.30 ± 1.18; P < 0.01) than in those with the Ff genotype (1.32 ± 0.96). The z scores of the bone phenotypes of the femoral neck from the athletic groups with both VDR genotypes are shown in Fig. 2. All bone phenotypes were significantly greater in the athletes than in the controls irrespective of the VDR genotype. There was no difference in the z score of the femoral neck volume between the athletes with the FF genotype and those with the Ff (1.40 ± 1.32 and 0.97 ± 0.78, respectively; P = 0.20), in contrast to the genotype-dependent volumetric adaptation observed at the lumbar spine. However, the z score of BMC in the athletes with the FF (2.92 ± 1.14) was significantly greater (P < 0.01) than that with the Ff genotype (1.98 ± 1.10). Concerning the BMD of the femoral neck in the athletes, the FF genotype (2.05 ± 0.09) had slightly greater z score than the Ff (1.54 ± 0.76), but the trend did not reach statistical significance (P = 0.07).

DISCUSSION

The skeleton is a highly adaptable tissue that responds to strain produced by external stimulus. Exercise, particularly with impact loading, is one important factor by which dramatic improvements in bone homeostasis as a whole can be produced. However, the vast majority of published studies have emphasized main effects and group differences rather than sources of individual variability such as potential diversity in genes. Focusing on the interaction between VDR polymorphism and impact loading on the bone geometric index, the present study demonstrated that BMC at the lumbar spine and femoral neck in young male athletes engaged long term in high-impact sports depended on the VDR genotypes distinguished by endonuclease Fok I. Further observation emphasized that the spinal volume of the athletes was greater than that of the nonathletic controls only in the subjects with the FF genotype but not in Ff.

Numerous researchers have reported site-specific BMDs with increments in skeletal sites (i.e., hip and lumbar spine) subjected to impact loading in young competitive athletes (9, 28, 32, 33, 45). In contrast to

Table 3. Prevalence of VDR genotype and physical characteristics of the subjects

<table>
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<th>Control</th>
<th>Athlete</th>
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<tr>
<td>FF</td>
<td></td>
<td></td>
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<tr>
<td>Frequency, %</td>
<td>34.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Exercise career, yr</td>
<td>1.1 ± 1.0</td>
<td>8.2 ± 0.9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>19.8 ± 1.1</td>
<td>20.6 ± 1.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.8 ± 5.6</td>
<td>177.7 ± 5.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.9 ± 9.4</td>
<td>70.9 ± 7.1</td>
</tr>
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</table>

Values are means ± SD. VDR, vitamin D receptor; FF, homozygous for absence of endonuclease Fok I restriction site; Ff heterozygous for restriction site.
the well-studied effect of exercise with high-impact loading on BMD in loaded bones, the potential consequence for bone geometry has not been equally established. Our cross-sectional study found that the athletes, as a whole, had a significant elevation of BMC and density at lumbar spine and femoral neck, similar to a previous report of enlarged bone area of the pelvis and legs in young male soccer players (51). Interestingly, however, there was no significant volumetric adaptation in the lumbar spine to impact loading in the athletes with the FF genotype of the VDR. A larger bone size, and subsequently a greater cross-sectional area, increases one index of bone strength (polar moment of inertia) and resistance to external load (36). On the other hand, the smaller size of vertebral bone could be one risk factor for spinal fracture (40, 41). Thus, as observed in our present cross-sectional study, the phenomenon of enlarged spinal volume only in the athletes with the FF but not in those with the Ff genotype may suggest that the FF of the VDR gene makes a positive contribution to reducing fracture risk through impact loading exercise.

The genotype-dependent difference in enlargement of bone volume shown in the lumbar spine failed to be significant in the femoral neck between two athletic groups. Although impact loading puts great stress preferentially on the lower extremities and lumbar spine, the loading patterns probably differ somewhat between these skeletal sites. Also, in addition to the different tempo of growth in bone structure between the trunk and leg (5), there may be regional dependencies in the biological system of bone maintenance. Our results implied that the interaction between impact loading and VDR polymorphism on bone phenotype might be site specific. On the other hand, the z score of the BMC of the lumbar spine and femoral neck was greater in athletes with the FF genotype compared with those with Ff. Therefore, the bone of the subjects carrying the FF acquired more bone mineral through mechanical adaptations to the impact loading.

Our previous study investigating the contribution of the VDR genotype on total body BMD among athletes suggested that the FF genotype is more responsive to impact loading in acquiring total BMD (30).

Table 4. Comparison of adjusted BMD, BMC, and bone volume

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<tr>
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<th>Athlete</th>
<th>Interaction Term, ( P )</th>
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<tbody>
<tr>
<td>Lumbar spine</td>
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<tr>
<td>BMD, g/cm²</td>
<td>1.012±0.208</td>
<td>1.036±0.095</td>
<td>1.215±0.126, 1.176±0.104, 0.19</td>
</tr>
<tr>
<td>BMC, g</td>
<td>16.7±2.4</td>
<td>17.8±2.2</td>
<td>22.3±2.9*, 20.7±2.1, 0.01†</td>
</tr>
<tr>
<td>Volume, cm³</td>
<td>66.8±6.4</td>
<td>69.0±7.2</td>
<td>77.2±9.1*, 71.6±7.1, 0.02†</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD, g/cm²</td>
<td>0.981±0.115</td>
<td>1.001±0.127</td>
<td>1.217±0.104, 1.197±0.111, 0.44</td>
</tr>
<tr>
<td>BMC, g</td>
<td>5.0±0.5</td>
<td>5.1±0.7</td>
<td>6.6±0.6, 6.5±0.8, 0.44</td>
</tr>
<tr>
<td>Volume, cm³</td>
<td>13.7±1.7</td>
<td>13.6±2.4</td>
<td>16.1±2.2, 15.9±1.9, 0.99</td>
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Values are means ± SD. *Statistically significant difference from the Ff genotype (\( P < 0.01 \)). †Interaction between exercise and genotype was evaluated by multivariate ANOVA (\( P < 0.01 \)).
present study, we did not detect clear differences in regional BMD at loaded sites between the VDR genotypes among young athletes. BMD values, which represent the quotient of BMC and bone area, might be misleading when the increases in bone size are of the same magnitude or higher than the increases in BMC (44). A study in late-adolescent athletic women with high-impact loading at the lower limbs observed that rope skippers had a significantly larger bone area but similar BMD in the lower extremity compared with soccer players (32). It is possible that the effect of bone compression by impact force may be manifested as a dimensional variation without reflecting the difference in the BMD, at least during growth. Similarly, at loaded sites in the young male athletes, the influence of genetic variance in bone response to impact loading may emerge as differences in BMC or bone volume, rather than those in BMD.

As a global concept, bone can adapt to external load by changing its microstructure, mass, and size in a way that keeps the internal effective strain levels within a physiologically reasonable and safe range (13). However, taken together, our present observations in athletes with different VDR genotypes suggested that the FF might relate to producing stronger bone structure by impact loading than the FF genotype. Moreover, even if athletes engaged in the impact-loading sports have the same level of increased BMD compared with nonathletic controls, the VDR polymorphism could provide potential heterogeneity in the bone geometric characteristics. There may be an independent mechanism of bone adaptation to impact loading through variations in candidate gene(s) that influences bone homeostasis, although the extent to which genetic factors contribute to the differences in the bone geometric response remains unclear. Further research to resolve the function of the VDR gene in the mechanotransduction system will lead to understanding of the gene-environment interaction in bone physiology.

The VDR gene has been postulated to be a predictor of individual differences in BMD (15, 29). A polymorphism at the translation initiation site of the VDR gene, in particular, has received great attention because the C-to-T transition would lead to structural change of encoded protein (2). As a result, this polymorphism may possess a more obvious theoretical mechanism to affect VDR biological function (2, 10, 23, 50). A relationship between BMD and the VDR genotypes defined by Fok I has been supported by many observations that the FF subjects have greater BMD than the ff or FF (1, 2, 16, 20, 25, 26), although the association is still controversial (12, 20, 52). In our study, no bone phenotype including BMD in healthy young Japanese men, except for the athletes, depended on their VDR genotype. This conflict may be explained by the hypothesis that the VDR variance may determine the sensitivity of bone responses to environmental stimuli. In fact, we previously found an interesting possibility that bone metabolic response to exercise is mediated differently between carriers and noncarriers of the f allele of the VDR (47), suggesting functional differences between the genotypes, given gene-environment interaction. Therefore, our present findings support the idea that the diversity of the VDR gene may play an important part in the mechanism of individual variability of bone trainability rather than as a prediction factor of BMD itself.

In summary, long-term high-impact loading increased size and BMC of bone at loaded sites, and the polymorphism of the VDR gene at the translation initiation site seemed to modify responses of these geometric changes of the bone. Our results suggest that the bone phenotype of individuals with the FF genotype adapt to impact loading by producing stronger bone structure than those with the FF do. The two isoforms of the VDR, which originate from a C-to-T transition within exon 2, may act differently in their biological function through external stimulus, resulting in the prediction of bone structure, as mentioned in many previous reports. It must, therefore, be emphasized that the interindividual allelic variance of gene(s) should not be ignored in understanding the intricate processes that determine human phenotype through exercise, because any physical response can be regulated by multiple factors in the gene-environment interaction.

REFERENCES


