Association of physical activity and bone: influence of vitamin D receptor genotype

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ABSTRACT
BLANCHET, C., Y. GIGUÈRE, D. PRUD’HOMME, M. DUMONT, F. ROUSSEAU, and S. DODIN. Association of physical activity and bone: influence of vitamin D receptor genotype. Med. Sci. Sports Exerc., Vol. 34, No. 1, 2002, pp. 24–31. Purpose: The aim of the study was to investigate the interaction between leisure physical activity and a BsmI polymorphism at the vitamin D receptor (VDR) gene on the modulation of bone mineral density (BMD). Methods: We studied 575 unrelated healthy postmenopausal women. Lumbar spine and femoral neck BMD were measured by dual-energy x-ray absorptiometry (DXA), and results were expressed as age- and weight-adjusted (Z-score). VDR /BsmI genotype was determined by polymerase reaction chain on peripheral blood leukocytes. Results: Overall, no significant association was found between the level of leisure physical activity or VDR genotypes and adjusted BMD at both bone sites. However, in active women, there was a trend for an association between VDR genotypes and adjusted BMD at the lumbar spine. Active women, who exercised three times or more a week, carrying the “bb” genotype had a lower BMD at the lumbar spine than active women carrying “BB” genotype (ANOVA; P = 0.04). No significant difference in crude or adjusted BMD at both bone sites was found between VDR genotypes in sedentary or moderately active women. Furthermore, classification of women according to the median-age of the sample (63.1 yr) revealed a significant interaction between the level of leisure physical activity and VDR genotype on adjusted lumbar spine BMD in the older active postmenopausal women (N = 137). Older active women carrying the “bb” genotype showed a lower adjusted BMD at the lumbar spine compared with active women carrying the “BB” genotype (P = 0.007). Conclusion: These results suggested that gene-environment interactions such as leisure physical activity and VDR genotype may play a role in maintaining the BMD at the lumbar spine in active postmenopausal women, especially in older active women. Key Words: BONE LOSS, GENE-ENVIRONMENT INTERACTION, PHYSICAL ACTIVITY, POSTMENOPAUSAL WOMEN, VITAMIN D RECEPTOR POLYMORPHISM.

Osteoporosis is a multifactorial disease involving genetic and environmental factors. Results from family and twin studies showed that genetic factors may account for as much as 60 to 80% of the inter-individual variation observed in the bone mineral density (BMD) (33). Many allelic association studies reveal that genetic polymorphisms with small functional differences may increase or decrease risk of osteoporosis (16). A few years ago, polymorphisms of the vitamin D (VDR) receptor loci have been proposed as genetic candidate for their involvement in the development of osteoporosis as a result of their central position in the control of calcium homeostasis. In 1994, Morrison and coworkers (23) reported that common allelic polymorphisms in the VDR gene could explain up to 75% of the total genetic BMD variation in healthy Australian twins. These investigators studied a VDR /BsmI polymorphism (“B” for the absence of the polymorphic site and by “b” for its presence) in twins as well as in unrelated postmenopausal women and found an association between VDR genotype and BMD: “b” homozygotes (bb genotype) had a significantly higher BMD compared with “B” homozygotes (BB genotype, the less common genotype). Women with the “Bb” genotype had an intermediate BMD. Since then, considerable interest has been focused on reproducing these findings in different populations but not all studies confirmed this association (2,8,24). Some investigators (12,35) found a significant association between VDR genotype and BMD, whereas others (4,13) did not. Furthermore, Uitterlinden and coworkers (35) found an opposite association between BMD and VDR genotypes; women carrying the “BB” genotype had a higher BMD compared with women carrying the “bb” genotype. Recently, Morrison et al. (25) were unable to confirm their results in a larger twin study, but they maintained that the association between the BMD and the VDR genotypes still holds in unrelated postmenopausal women. Part of the controversy over the potential association between VDR polymorphism and BMD could be explain by differences in risk and environmental factors (i.e., age, weight, postmenopausal status, dietary habits, sun exposure, physical activity, etc.) between subjects recruited from different study designs and between populations, and gene-environment interactions. Lastly, the role of gene-environment interaction on physiological effects of exercise has
been an area of interest among physiologists. Studies in the field of exercise physiology brought insight over the role of genetics on physical fitness stamina. These studies highlight the genetic variability of individual differences in response to training (6). It is well documented that physical activity brings a significant positive skeletal effect during adolescence (34) and on the acquisition of peak bone mass in young adulthood (18). In postmenopausal women, most longitudinal studies indicated that moderate exercise might slow the rate of bone loss (28,30). Recently, Wolff and colleagues (36), in a meta-analysis, concluded that an exercise training program had the capacity to prevent or reverse bone loss at the lumbar spine and femoral neck of pre- and post-menopausal women by almost 1%. However, the exact relationship between physical activity and BMD remains unclear. Until now, investigators have attributed differences observed in BMD responses to exercise to factors such as age and the diversity in exercise protocols (nature of exercise, duration, frequency, and intensity) as well as methods and sites of bone measurements.

Until now, there have been little data on physical activity and BMD taking into account the genetic factors. Recent cross-sectional studies among premenopausal women suggested that the interindividual allelic variation in the VDR gene could modulate the influence of physical activity on BMD (20,31). Therefore, the aim of this study was to investigate the potential interaction between the level of leisure physical activity and VDR BsmI polymorphism as a determinant of BMD in postmenopausal women.

MATERIALS AND METHODS

Subjects. Recruitment was achieved through voluntary response to local newspaper advertisement for a study on genetic and environmental factors affecting BMD in postmenopausal women. Overall, 710 women, recruited by advertisements in local newspapers, were interested to participate in the study. All subjects were French Canadian Caucasian women living in the Québec City metropolitan area. Ninety-five percent of these women did meet the entry criteria, which were good health, no clinical signs of bone mineral disease, and no use of medications that could interfere with bone metabolism, except for hormone replacement therapy (HRT). Therefore, 675 unrelated women were recruited, and informed and written consent was obtained. During their visit to the center, each subject answered a detailed questionnaire, with assistance of a qualified interviewer, covering family, medical, and surgical history (menopausal status), medications, and lifestyle (physical activity, HRT, calcium intake, etc.). Weight and height were recorded while the women were dressed in light indoor cloths with shoes removed. Ten mL of blood was obtained by a venous puncture. After all steps of VDR genotype analysis, 575 unrelated postmenopausal women aged between 42 and 85 yr were included in the study. The Medical Ethics committee of St-François D’Assise Pavilion Hospital approved the protocol.

Menopausal status. The menopausal status of subjects, such as age at menopause and the number of years since menopause, was obtained by the questionnaire. They were considered to have attained menopause if they had not had their menses for at least 1 yr before recruitment. In regard to hormone replacement therapy (HRT), women were asked if, at the time of recruitment, they were taking HRT and for those who were receiving HRT, for how long they had been using this medication.

Menopausal transition is closely related to the manifestation of osteoporosis, which could be subdivided into two distinct models. Type I (postmenopausal) osteoporosis which typically affects trabecular bones becomes apparent in women within 5–10 yr after menopause and is the consequence of increased bone remodeling secondary to estrogen deficiency. Type II (aged-related) osteoporosis affects both sexes but is twice as common in women than in men and occurs mainly in individuals aged over 70 yr. Type II osteoporosis affects both cancellous and cortical bones. Any evaluation of the presence or the absence of fracture, such as spine radiographs, was performed in this present study; therefore, to adequately define osteoporosis, we divided the total sample of women according to the median age (63.1 yr), which represents the distribution of age of the population and, furthermore, a close cut point of these two patterns of bone loss.

Lifestyle. Lifestyle was evaluated using a questionnaire derived from the Mediterranean osteoporosis (MEDOS) study questionnaire (9). Physical activity was estimated by a questionnaire measuring patterns of exercise behavior (17). This questionnaire showed that self-reported measurement relative to exercise habit during leisure time was a valid method for assessing exercise behavior of a population. The question relating to physical activity was “How often did you participate in one or more physical activities of 20–30 min duration per session during your leisure time within the past 4 months?” The choices given were 1) not at all, 2) less than once a month, 3) about once a month, 4) about two to three times a month, 5) about one to two times a week, and 6) three or more times a week. For the purpose of the analysis, women were classified into three groups according to their physical activity levels: sedentary (less than three sessions a month (answer 1 to 4)), moderately active (one to twice a week (answer 5)), and active (three or more sessions a week (answer 6)).

Daily dietary calcium intake of the previous week was evaluated by the questionnaire. Furthermore, women were asked whether, in the past month, they were taking calcium supplements. According to these two questions, the total daily calcium intake was estimated.

Bone densitometry. BMD was measured at the lumbar spine, from level L2 to L4 inclusive and at the femoral neck (FN) by using dual-energy x-ray absorptiometry (DXA) (DPX-L, Lunar Radiation Corporation, Madison, WI, software version 3.2). This apparatus uses an x-ray source with automatic positioning at the selected sites and software to calculate the BMD. A trained technician in nuclear medicine took all measurements, and the same
TABLE 1. Characteristics of women.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Sedentary</th>
<th>Moderately Active</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.3 ± 7.0</td>
<td>63.4 ± 7.9</td>
<td>62.5 ± 5.8</td>
<td>63.5 ± 6.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.7 ± 12.4</td>
<td>65.8 ± 13.4</td>
<td>66.0 ± 12.9</td>
<td>63.4 ± 11.3</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>26.2 ± 4.8</td>
<td>26.8 ± 5.3</td>
<td>26.6 ± 5.1</td>
<td>25.7 ± 4.2</td>
</tr>
<tr>
<td>HRT (%)</td>
<td>48.9</td>
<td>48</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>Years HRT††</td>
<td>7.9 ± 7.3</td>
<td>8.7 ± 8.4</td>
<td>8.2 ± 6.8</td>
<td>7.7 ± 6.9</td>
</tr>
<tr>
<td>Calcium intake (mg·d⁻¹)</td>
<td>828 ± 517</td>
<td>717 ± 481</td>
<td>813 ± 520</td>
<td>901 ± 527</td>
</tr>
</tbody>
</table>

Values denote means ± SD.
HRT††, % of subjects under hormone replacement therapy at recruitment.
Years HRT††, among subjects who were on HRT.
* P = 0.05, active vs sedentary; ** P = 0.03, active vs sedentary; † P = 0.001, active vs sedentary.

experienced physician revised every scan. The long-term reproducibility of the apparatus, evaluated on a daily basis using a standard bone phantom, gave a coefficient variation smaller than 1%. In vivo precision was evaluated by repeat measurements in 26 subjects; the average CV was 1.7% at the lumbar spine and 2.2% at the femoral neck. Furthermore, four women were considered as isolated outlier for either BMD at the lumbar spine or femoral neck and were eliminated from all analysis.

Genotyping. Briefly, genomic DNA was isolated from peripheral blood leukocytes by a mini-method necessitating only 200 μL of whole blood where all steps are processed in a single 1.5-mL tube. Isolated DNA (5–7 μg) was resuspended into 100-μL TE 20:5 buffer (20 mM Tris, 5 mM EDTA), heated at 65°C for 4 h, and stored at 4°C until PCR was performed. The VDR-BsmI polymorphism was amplified by PCR and digested as described previously. After BsmI digestion, genotypes were visualized by ethidium bromide after migration in a 2% agarose gel electrophoresis. Absence of the polymorphic site (“B” allele) resulted in a 850-bp fragment, whereas presence of the polymorphic site (“b” allele) resulted in 700-bp and 150-bp fragments. Three independent readers interpreted results and all samples with discordant readings were rejected. Concordance rates were higher than 96%. The genotype analysis determined the final number of women eligible for this study. Finally, 575 unrelated Caucasian postmenopausal women were included in this cross-sectional study.

Statistical methods. Data are expressed as the mean ± standard deviations unless specified otherwise. Analysis of variance (ANOVA) was performed, followed by Student’s t-test with the Bonferroni correction for subgroup comparisons. A P-value lower and equal to 0.01 was considered statistically significant, whereas P-values between 0.01 and 0.05 were considered as suggestive evidence. Differences in proportions were compared by Fisher’s exact probability test (2 × 2 contingency tables) or Pearson’s chi-square analysis. Analyses of the correlation between BMD and age, number of years postmenopause (ypm), height, weight, body mass index, and age at menarche using covariance analysis (ANCOVA) revealed that age and weight were the most highly correlated variables to bone density (P ≤ 0.0001). L2–L4 and FN BMD were adjusted for age and weight only, as the contribution of other variables were nonsignificant after adjustment for age and weight. Then we evaluated whether the age-and-weight-adjusted L2-L4 and FN BMD derived from formulas available from the manufacturers could be applied to our sample. We found that weight was still highly correlated with the formula-adjusted BMDs (P ≤ 0.0001), so we adjusted bone density measurements at both sites from our data instead of using the manufacturers’ formulas. Furthermore, we investigated potential associations between bone density measurements and genotypes and physical activity levels for the whole sample (N = 575) and according to the median age, in younger (age ≤ 63.1 yr, N = 287) as well as in older (age > 63.1 yr, N = 288) allowing reasonable power in both subgroups. All analyses were performed using JMP 3.0 statistical software package (SAS Institute, Cary, NC) and Statview 5.0 package (SAS Institute).

RESULTS

General results. The subjects’ characteristics according to leisure physical activity level and to VDR genotype are presented in Table 1. Classification of the sample according to

TABLE 2. Frequencies of VDR genotypes according to physical activity levels.

<table>
<thead>
<tr>
<th>VDR Genotypes</th>
<th>Sedentary</th>
<th>Moderately Active</th>
<th>Active</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>24 (13.6)</td>
<td>24 (19.4)</td>
<td>52 (18.9)</td>
<td>100 (17.4)</td>
</tr>
<tr>
<td>Bb</td>
<td>62 (35.2)</td>
<td>49 (39.5)</td>
<td>116 (42.2)</td>
<td>227 (39.5)</td>
</tr>
<tr>
<td>bb</td>
<td>176 (100.0)</td>
<td>124 (100.0)</td>
<td>275 (100.0)</td>
<td>575 (100.0)</td>
</tr>
<tr>
<td>Allele frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>69 (39.0)</td>
<td>49 (39.5)</td>
<td>105 (38.3)</td>
<td>224 (39.0)</td>
</tr>
<tr>
<td>b</td>
<td>108 (61.0)</td>
<td>75 (60.5)</td>
<td>169 (61.7)</td>
<td>351 (61.0)</td>
</tr>
</tbody>
</table>

Values are numbers of subjects.
(1) Percentage of subjects with each genotype/allele.
leisure physical activity levels showed that one third of women were sedentary, 22% were moderately active and 48% were active. After this stratification, a significant difference was observed among the three groups for body mass index (BMI: kg m⁻²) (ANOVA; P = 0.03) and total daily calcium intake (ANOVA; P = 0.001). Sedentary women had a higher BMI and a lower daily calcium intake than active women did. No significant difference in women’s characteristics was found between VDR genotypes. Also, no significant difference in the prevalence of use of HRT, of women with hysterectomy, or in lifestyle factors such as cigarette smoking or alcohol intake between the three groups of leisure physical activity or VDR genotypes (data not shown).

Table 2 shows the distribution of VDR genotype frequencies according to leisure physical activity levels. In the total sample (N = 575), 17.4% were homozygous for the “B” allele (BB genotype), 43.1% were Bb heterozygous, and 39.5% were homozygous for the “b” allele (bb genotypes). The frequency of the “b” allele was thus 61% and 39% for the “B” allele. No significant difference in genotype and allele frequencies were found among the three physical activity levels in the total sample (χ² = 7.2; P = 0.12).

Table 3 shows the characteristics of women according to VDR genotype and leisure physical activity levels. No significant difference was observed among those bearing either the “BB” or “Bb” genotypes. However, in women carrying the “bb” genotype, sedentary women had a higher BMI than active women (ANOVA; P = 0.02) and a lower daily calcium intake (ANOVA; P = 0.004). Although weight and BMI were highly correlated (r = 0.92), body weight was more associated with BMD than BMI (r = 0.33 and 0.25, respectively), and, therefore, weight was used exclusively in subsequent analyses.

**BMD.** BMD according to leisure physical activity levels or VDR genotypes separately are shown in Table 4. Crude and adjusted (Z-score) means lumbar spine and femoral neck BMD were not significantly different between the three levels of leisure physical activity. On the other hand, a trend was observed between VDR genotypes for the crude means BMD of the lumbar spine as women carrying VDR “bb” had a lower lumbar spine BMD than women carrying the “BB” and “Bb” genotypes (ANOVA; P = 0.04). However, these trends disappeared when BMD was adjusted for age and weight (Z-score).

Because we observed an association between BMD and age, weight, and calcium intake in previous results, all further analysis of BMD was adjusted for these parameters. When subjects were grouped according to their VDR genotypes, no significant difference was found between women with different leisure physical activity levels within each VDR genotype at the lumbar spine or at the femoral neck BMD (ANOVA; lumbar spine: BB: P = 0.56, Bb: P = 0.81, bb: P = 0.55; femoral neck: BB: P = 0.44, Bb: P = 0.41, bb: P = 0.99) (Fig. 1). However, a trend was observed between VDR genotypes and L2-L4 BMD Z-score in active women only (ANOVA; P = 0.04), where active women carrying the “bb” genotype had a lower BMD Z-score than those bearing the “BB” genotype. No such result was observed at the femoral neck.
We thus further analyzed the relationship between leisure physical activity levels, VDR genotype, and BMD in younger and older postmenopausal women separately in accordance with the type I and II osteoporosis classification. Figure 2 shows the mean lumbar spine adjusted BMD measures in women with varying VDR genotypes and leisure physical activity levels after stratification according to the median age of the sample (age $< 63.1$ and age $> 63.1$ yr), thus splitting the sample in two halves ($N = 287$ and 288). In the youngest age group, no significant difference was observed between mean-adjusted L2–L4 BMD measures within each leisure physical activity level or VDR genotype. In the oldest group, no significant difference in mean-adjusted L2–L4 BMD was found within each VDR genotype for the three leisure physical activity levels. However, active women carrying the “bb” genotype had a significantly lower adjusted BMD L2–L4 than those with another VDR genotype (ANOVA; $P = 0.02$). Furthermore, when compared with those carrying the “BB” genotype, the adjusted BMD difference was much larger ($P = 0.006$). Between sedentary and moderately active subgroups, no significant difference in means adjusted BMD was found. Finally, we observed no significant association between means adjusted BMD at the femoral neck and the VDR genotype or leisure physical activity level—or both—as stratified by the age median (data not shown).

**DISCUSSION**

In this study of healthy postmenopausal women, our results suggest that VDR genotypes may influence the relationship between leisure physical activity level and lumbar BMD especially in older postmenopausal women. On the other hand, no difference was observed in femoral neck or lumbar spine BMD with regards to VDR genotype or leisure physical activity levels. However, after stratification of the sample of women according to leisure physical activity levels and VDR genotype, a trend of significant difference in BMD at the lumbar spine was found between VDR genotypes in active women only. A possible benefit of leisure physical activity was observed in women carrying the “BB” genotype compared with women carrying the “bb,” whereas no strong benefit was observed in women carrying the “Bb” genotype. When stratified by age, this effect was limited in older women and was more important than after the analysis of the whole group. This suggests that for postmenopausal women bearing the “B” allele, regular leisure physical activity such as walking may delay the rate of bone loss as compared with those with only “b” alleles (“bb” genotype). However, this interpretation must be taken with caution. The presence of confounding factors related to both physical activity and VDR polymorphism may act on BMD of postmenopausal women.

Also, potential selection bias had to be taken into consideration. The homogeneity of our cohort seems very
important in reducing confounding variables and unmasking some association. The French Canadian population of Quebec is a young population (10–13 generations) that was established by about 8000 founders, showed a rapid demographic expansion in relative isolation due to little immigration and is genetically well defined (7). A high concentration of common ancestors of the current Quebec Francophone population was settled before 1680. The genetic contribution of these ancestors is estimated to about two thirds of the present Quebec Francophones’ gene pool, much more than what was found in similar studies on the contribution of the first founders of other Caucasian populations: 13% for the founders of the Finnish population of Sottunga (27) and 17% for the founders of the Vallée de la Valserine in the French Jura (19). The contribution of the first founders to the French-Canadian genetic pool became sufficiently large to withstand influx of later migrations. For these reasons, the French population of Quebec is believed to show a lower degree of population/genetic stratification than admixed cosmopolitan urban populations (15).

Equally, the distribution of the VDR BsmI genotypes of our cohort is consistent with that found for other Caucasian women (British-Irish population of Australia (23) and United States (1)). Even after stratification of the sample according to their leisure physical activity levels, no significant difference was observed in allele frequencies between active and sedentary women.

With regard to the general characteristics of the women in this study, they were comparable to those of women randomly included in the National Quebec Survey (32). The proportion of overweight women (BMI > 27) was comparable to the Quebec survey sample (22.8% vs 22.0%). After stratification according to leisure physical activity levels, some differences in BMI were observed. Sedentary women had a greater BMI and had a lower total daily calcium intake than active women. These findings were expected, as reported in few studies, because active women tend to be more health concerned. Also, 49% of the sample received hormone replacement therapy, which is slightly more than the 35% reported by the Quebec survey. These percentages recorded a few years ago might have increased over the last few years, mainly because postmenopausal women get more information about menopause and therapeutics alternatives. However, in this cross-sectional study, there were no significant differences in the number of women taking or not hormone replacement therapy among the VDR genotypes (P = 0.30) or physical activity levels (P = 0.23) in the whole sample or in subgroups according to the median age.

Furthermore, the distribution of the lumbar spine and femoral neck BMD of women included in this present study was not different than in a population-based sample of French Canadian women (2) and thus suggests good representatives.

With respect to leisure physical activity levels, our results indicate that 48% of women exercised 20–30 min or more, three or more times per week. This is in agreement with Quebec survey, which found that among women aged 45 and older, 38.4% of them reported regular physical activity. Walking was the main leisure physical activity reported by women in different age categories evaluated in this survey as well as in our study. These similarities in the nature of

![FIGURE 2—Lumbar spine Z-scores BMD in relation to VDR genotypes and leisure physical activity levels according to age groups. *63.1 years = median age. Values denote means ± SE. BMD are adjusted for age and weight (Z-score) and calcium intake. Aged less than 63.1 years: no significant difference. Aged more than 63.1 years: * Active women; P = 0.021 after the Bonferroni correction.]
exercised suggest that our sample probably reflects adequately the general population of postmenopausal women and is probably not strongly biased with respect to leisure physical activity levels. Finally, as our population was not randomly selected, women who decided to participate into the present study could be more healthy and more health concerned or may have a strong family history of osteoporosis that motivated them to participate. These potential selection biases could not be eliminated, but we believe they should not influence the internal validity of the study. However, our results should be taken cautiously and longitudinal studies investigating the effect of VDR genotypes on BMD in a large sample size of postmenopausal women after weight-bearing exercise (such as walking) programs should be undertaken.

It is well documented that postmenopausal (type I) as well as age-related bone loss (type II) are characterized by loss of trabecular bone mass and trabecular connectivity, thinning of cortical bone, and also lack of capability for periosteal apposition (21). Our results are in agreement with the dynamics of bone physiology. The relative contents of trabecular bone at the lumbar vertebra is about 66–90% compared with only 25% in femoral neck (11). The rest is compact bone. Rates of remodeling in trabecular bone are proportionally higher throughout life and may normally be 5–10 times higher than cortical bone remodeling rates in adults (11). All measurement of the lumbar spine were done by an posteroanterior scan, which includes contribution from the cortical bone and the spinous processes, as well as the trabecular bone of the vertebral body. The precision of a posteroanterior measurement is 1–1.5% for the spine (14). We found BMD modifications at the lumbar spine only in older women. No significant difference was observed in BMD at the femoral neck.

In the literature so far, it is presumed that the mechanical load applied to bone is transduced through the skeleton via a mechanical signal that is detected by certain cells. Two types of cells are candidates for detecting these mechanical signals, bone lining cells (of osteoblastic origin) and osteocytes. Osteocytes seem the most mechanosensitive cells in bone. These cells are connected to each other, to osteoblasts, and to bone-lining cells by means of cell processes residing in the canaliculi of unmineralized bone matrix, and these conduits allow for communication between cells. Changes in flow of interstitial fluid through osteocytic canaliculi, either by an electrical potential or a direct mechanical effect over the surface, will produce a signal that modulates bone formation (osteoblasts) or resorption (osteoclasts) (10). Therefore, weight loading plays an important role in the maintenance of trabecular connectivity (through the remodeling process), in the orientation of the trabeculae, and in the periosteal apposition (through the remodeling process). Loading is important for the maintenance of bone strength during normal aging (10). Our results revealed significant association between physical activity levels and/or VDR genotypes at the lumbar spine only. No association at the femoral neck was observed. Our hypothesis, based on our recent results, which can explain such finding, is that exercise acted primarily on the preservation on the bone architecture and bone strength. Therefore, the impact of exercise as bone protection of the trabecular connectivity could be less important at the femoral neck because it is composed of only 25% of trabecular bone compared with almost 90% in vertebra. Furthermore, if an interaction of genetic factors and physical activity is present, such as we found at the lumbar spine, it will be much easier to observe it in bone with higher trabecular bone content.

Furthermore, the difference observed in response to alter mechanical environment could be due to differences in response to loading signals or differences in other hormonal or metabolic factors that impact on bone formation. VDR is an intracellular steroid receptor and it is conceivable that bone cells’ proliferating response to mechanical strain may also involve VDR because receptors for 1,25(OH) 2 D 3 are present in osteoprogenitor cells, osteoblasts precursors, and mature osteoblasts (26).

Most recently, studies among premenopausal women indicated that VDR genotypes and lifestyle factors were determinants of BMD (31). Our results were in concordance with these findings. Furthermore, recent studies revealed that VDR alleles have a weak effect at the femoral neck and a stronger effect at the lumbar spine and that exercise could be a potent osteogenic stimulus in young postmenopausal women but may not be sufficient to bring changes in BMD in older postmenopausal women (3,36). This cross-sectional study supports earlier studies suggesting that the association between leisure physical activity levels and BMD may have genetic components and that these parameters could share a common genetic basis (5). These findings could help clarify conflicting results observed in previous studies investigating the effect of exercise training on BMD in women, as well as contradictory findings on the association between VDR genotype and BMD. Until now, these discrepancies were attributed to difference in the exercise program (type, intensity, frequency, and duration), or in the characteristics of subjects (age, diet, and hormonal status). However, the controversy might be explained, at least in part, by genetic factors as well as their interactions with the level of weight-bearing activities.

In conclusion, the lack of clear evidence in the literature for a benefit of leisure physical activity in older postmenopausal women could be due to divergent effects of exercise on lumbar spine BMD in these women due to their VDR genotypes. Indeed, older active women carrying the “BB” genotype could benefit more from leisure physical activity as opposed to women carrying the “bb” genotype. In the present study, women with the “BB” genotype had a much higher lumbar spine BMD. This difference of 0.77 SD corresponds to a 1.8-fold decrease risk of fracture (22). Even if only 17% of women bear this genotype, this could nevertheless have an interesting public health impact, notwithstanding the other benefits of leisure physical activity on health and aging.

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