Experimental Physiology

Vitamin D receptor \textit{FokI} genotype influences bone mineral density response to strength training, but not aerobic training

Karma M. Rabon-Stith\(^1, 2\), James M. Hagberg\(^1\), Dana A. Phares\(^1\), Matthew C. Kostek\(^1\), Matthew J. Delmonico\(^1\), Stephen M. Roth\(^1\), Robert E. Ferrell\(^3\), Joan M. Conway\(^4\), Alice S. Ryan\(^2\) and Ben F. Hurley\(^1\)

\(^1\)Department of Kinesiology, University of Maryland, College Park, MD 20742, USA
\(^2\)Division of Gerontology and Geriatric Research, Education, and Clinical Center, School of Medicine, University of Maryland, Baltimore, MD 21244, USA
\(^3\)Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15238, USA
\(^4\)Diet and Human Performance Laboratory, United States Department of Agriculture, Beltsville, MD 20705, USA

To determine the influence of the vitamin D receptor (VDR) gene \textit{FokI} and \textit{BsmI} genotype on bone mineral density response to two exercise training modalities, 206 healthy men and women (50–81 years old) were studied before and after \(~5–6\) months of either aerobic exercise training (AT) or strength training (ST). A total of 123 subjects completed AT (51 men, 72 women) and 83 subjects completed ST (40 men, 43 women). DNA was extracted from blood samples of all subjects and genotyping was performed at the VDR \textit{FokI} and \textit{BsmI} locus to determine its association to training response. Total body, greater trochanter and femoral neck bone mineral density (BMD) were measured before and after both training programmes using dual-energy X-ray absorptiometry. VDR \textit{BsmI} genotype was not significantly related to BMD at baseline or after ST or AT. However, VDR \textit{FokI} genotype was significantly related to ST- but not AT-induced changes in femoral neck BMD (\(P < 0.05\)). The heterozygotes (\(Ff\)) in the ST group approached a significantly greater increase in femoral neck BMD (\(P = 0.058\)) compared to \(f\) homozygotes. There were no significant genotype relationships in the AT group. These data indicate that VDR \textit{FokI} genotype may influence femoral neck BMD response to ST, but not AT.

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Corresponding author: K. M. Rabon-Stith: Department of Kinesiology, University of Maryland, College Park, MD 20742, USA. Email: kstith@umd.edu

Osteoporosis affects \(~20\) million Americans, of which \(~80\%\) are women, and costs US society as much as \$14 billion annually (Eddy, 1998). About 1.3 million fractures attributable to osteoporosis occur each year in people age 45 years and older, and this condition is responsible for 50\% of fractures occurring in women over age 50 years (Kanis et al. 1994).

There are two major types of bone: trabecular and cortical. Trabecular bone represents 20\% of the skeletal mass, and 80\% of the bone surface. It is located in the vertebrae and wrist, and in internal portions of the pelvis, skull and other flat bones. Cortical bone represents 80\% of the skeletal mass, is found primarily in the shaft of long bones, and forms the outer shell around cancellous bone at the end of joints and the vertebrae (Meier et al. 1984).

Trabecular and cortical bone are classified according to porosity. Cortical bone is much denser with a porosity ranging between 5\% and 10\% (Meier et al. 1984). It has a slow turnover rate, an age-associated loss of \(~2–3\%) per decade (Meier et al. 1984), and a high resistance to bending and torsion (Meier et al. 1984). Cortical bone provides strength where bending would be undesirable as in the middle of long bones. In contrast, trabecular bone is less dense, with porosity ranging from 20\% to 90\%. It is more elastic, has a higher turnover rate than cortical bone and a higher age-associated loss of bone mineral density (BMD) per decade (\(~12\%) (Meier et al. 1984).

Both trabecular and cortical bones are affected by osteoporosis. Compression fractures of the vertebrae (\(~8\%) and traumatic fractures of the wrist (\(~6\%) and femoral neck (\(~16\)) are most common (Kanis et al. 1994; Eddy, 1998). Fractures of the femoral neck, which is composed mostly of cortical bone, are associated with the greatest morbidity and mortality and most common in
the elderly population in which more than 90% of femoral neck fractures are caused by falls (Eddy, 1998).

The risk of fracture increases dramatically with age in both sexes, both because bones become more fragile and because the risk of falling increases. Roughly one in four (24%) women aged 50 years or older fall each year, compared to twice as many (48%) women aged 85 years or older; comparable figures for men are 16% and 35%, respectively (Eddy, 1998). These falls can result in fractures, and when they do the fracture is almost always caused by low bone mass or osteoporosis.

Advancing age is associated with a loss in BMD in both men and women, which may lead to osteoporosis (Mazess, 1982). Reducing the risk of bone fractures from osteoporosis involves preventing or delaying the loss of BMD. Both aerobic training (AT) and strength training (ST) have been recommended to retard age-related bone loss associated with osteoporosis (Saijo et al. 1991). However, studies in this area have produced disparate results and there is not a clear consensus on which exercise training modality is most beneficial for increasing, maintaining or preventing the loss in BMD with advanced ageing.

Several AT studies have shown an increase or no change in BMD (Aloia et al. 1978; Krolner et al. 1983; Peterson et al. 1991; Friedlander et al. 1995). In contrast, other AT studies show no significant effects (Cavanaugh & Cann, 1988; Nelson et al. 1994; Berard et al. 1997). With regard to ST, some investigators have reported that ST increases or preserves BMD (Nelson et al. 1991; Snow-Harter et al. 1992; Menkes et al. 1993; Lohman et al. 1995; McCartney et al. 1995; Ryan et al. 1995), whereas, others report no significant effects (Gleeson et al. 1990; Rikli & McManis, 1990; Pruitt et al. 1992). However, it is unknown how these two exercise training modalities compare to each other because there has been a complete absence of reports that have compared these two training modalities in the same study. For this reason, as well as for the importance of identifying effective interventions for age-associated bone loss, and because ST is considered the training modality of choice for the prevention and treatment of sarcopenia in the elderly, there is a need to compare the effects of AT with ST on BMD. However, it is important to note that BMD response to exercise training may be influenced by interindividual genetic variability (Bray, 2000).

The vitamin D receptor (VDR) gene has been targeted in BMD research (Morrison et al. 1994; Gong et al. 1999) because it regulates bone homeostasis through the vitamin D–endocrine system (Hannah & Norman, 1994; Haussler et al. 1998). The VDR gene is located on chromosome 12q and has several known allelic variants including a BsmI polymorphism in the intron between exons VII and IX and FokI restriction length polymorphism in exon II. Most studies have focused on the BsmI polymorphism (′B′ for the absence of the restriction site and ′b′ for the presence). The BsmI BB genotype has been associated with a small to modest decrease in bone mass, and a 2-fold increase in the risk of hip fracture compared with the bb genotype. However, it would not be predicted to have functional consequences because the polymorphism is located in the intron between exons VII and IX and it is not near the intron–exon borders. Thus, the function of the BsmI polymorphism is unclear.

In contrast, the FokI variant remains a candidate for functional polymorphism. The polymorphism resulting in a C-to-T transition within exon II of the VDR gene, defined by endonuclease FokI (′F′ for the absence of the restriction site and ′f′ for its presence), creates an upstream initiation codon and leads to the production of receptor proteins that differ in length by three amino acids (Saijo et al. 1991; Gross et al. 1996; Arai et al. 1997). This leads to the hypothesis that the shorter F allele may be more efficient in maintaining bone homeostasis (Arai et al. 1997; Gross et al. 1998; Colín et al. 2000). VDR FokI genotypes have been shown to influence BMD with and without environmental stimuli (Gross et al. 1996; Arai et al. 1997; Harris et al. 1997; Ames et al. 1999; Kanan et al. 2000; Katsumata et al. 2002). Thus, the primary purpose of this study was to determine the influence of VDR FokI and BsmI genotypes on the independent effects of AT and ST on BMD. A secondary purpose was to compare these two training modalities for their effectiveness for increasing regional and total body BMD, as assessed by dual-energy X-ray absorptiometry (DEXA).

Methods

Subjects

AT subjects. A total of 123 subjects (51 men, 72 women) recruited from the Washington, DC metropolitan area volunteered to participate in the study. The inclusion criteria were that subjects had to be between 50 and 80 years of age, non-smokers, without type 2 diabetes, physically inactive (< 20 min of continuous aerobic exercise < two times per week), no prior history of cardiovascular disease, a body mass index (BMI) of 37 kg m⁻², and, if female, were > 2 years post menopause. Women maintained their hormone replacement therapy (HRT) status (either on or not on HRT) constant for the duration of the study and this was controlled for in the statistical analysis. The University of Maryland College Park and University of Maryland at Baltimore Institutional Review Boards approved the study, and all subjects provided their written informed consent.

ST subjects. A total of 83 previously inactive subjects (40 men, 43 women) between 52 and 81 years of age who fitted the inclusion and exclusion criteria of the study volunteered to participate in the study. Although
one inclusion criterion was an age range between 50 and 80 years, an 81-year-old man was admitted to the study because he was 80 years old at the time of recruitment, but turned 81 by the time he started training. Subjects in this investigation were obtained from two different cohorts. The data from 20 subjects from an earlier investigation and 63 subjects from an ongoing trial were included in this analysis. There were no significant differences in age, training modality, or bone mineral density responses to training between the two cohorts. All subjects underwent a phone-screening interview, received medical clearance from their primary care physician and completed a detailed medical history prior to participating in this study. Some subjects also had a physical examination and a maximal exercise tolerance test on a treadmill in our laboratory prior to their participation. The inclusion criteria for all subjects were that they had to be non-smokers and free of significant cardiovascular, metabolic or musculoskeletal disorders that would affect their ability to safely perform heavy resistance exercise. Subjects who were already taking medications for at least 3 weeks prior to the start of the study were permitted into the study as long as they did not change medications or dosages at any time throughout the study. After all methods and procedures were explained, subjects provided informed written consent. The University of Maryland College Park Institutional Review Board approved the study.

Control subjects. Nine subjects tested twice at approximately the same time (before and after training) as the 20 ST subjects from an earlier investigation, were used to help control for the normal drifts in BMD. The control subjects were men between the ages of 51 and 71 years, who did no regular exercise between the two testing sessions and followed the same inclusion criteria as the two training groups. Only those who had not participated in a regular exercise programme for a minimum of 6 months prior to the study were included. They were free of cardiovascular disease, non-smokers, showed no indications of recent skeletal fracture and were not on any medications that would alter calcium or bone metabolism.

Experimental protocol

AT programme. Before and after exercise training, body composition, BMD and maximal oxygen uptake (\(V_{\text{O2 max}}\)) were assessed for each subject. The exercise training consisted of cycling, treadmill walking/running, arm ergometry and elliptical training. The training programme took place 3 days week \(^{-1}\) for 24 weeks, under the supervision of an exercise physiologist as previously described (Wilund et al. 2002). Exercise intensity and duration progressed from 50% to 70% \(V_{\text{O2 max}}\) and from 20 to 40 min during the first 10 weeks. Subjects trained for 40 min at 70% \(V_{\text{O2 max}}\) three times per week for the remaining 14 weeks and added a 45-to 60-min walk at home at the weekend.

ST programme. The ST programme for both cohorts consisted of the following six exercises using air-powered machines: leg press, chest press, leg curl, leg extension, upper back rowing and abdominal crunch. The leg press strengthens primarily the quadriceps and gluteals, the chest press strengthens the pectoral muscles, the leg curl strengthens the hamstring muscle group, and the knee extension exercise (machine is named leg extension) strengthens the quadriceps muscle group. Upper back rowing strengthens the latissimus dorsi and rhomboid muscles and abdominal crunch strengthens the abdominal muscles. The 20 subjects from an earlier investigation also performed two additional exercises, the lat pull-down and overhead shoulder press. The lat pull-down strengthens the latissimus dorsi muscles of the back and the shoulder press strengthens the muscles of the shoulder (primarily deltoids). For specific details on the location and axes of the muscle groups involved in each exercise the reader is referred to the following web site, www.cdc.gov/nccdphp/dnpa/physical/growing-stronger/exercise/more-exercises.htm

Detailed training protocols for both cohorts are described in detail by Delmonico et al. (2005). Briefly, each cohort completed two sets on all lower body exercises and one set on all upper body exercises, due to overlapping muscle groups that were exercised on some of the upper body exercises. The first four to five repetitions of each exercise were performed at a five repetition maximum (5 RM) resistance. The resistance was then reduced just enough to perform one or two additional repetitions. This process was repeated in the same set without altering the cadence of the repetitions until a total of 15 continuous repetitions were completed. This procedure allowed subjects to exert near-maximal effort on all repetitions and was made possible by thumb buttons on the exercise equipment, which allows for immediate changes in resistance at very small increments during each exercise, without having to stop the exercise. The first cohort trained for \(~24\) weeks and the second cohort trained for \(~2\) weeks, but there were no significant differences between the two cohorts in changes in strength or regional BMD. Although we recognize that the relatively short duration of training is a limitation of this study, we previously reported significant increases in femoral neck BMD with ST, and not in a control group, after only 16 weeks of training (Menkes et al. 1993).

Bone mineral density and body composition

For the AT, ST and control subjects, BMD and body composition were measured by DEXA using fan-beam technology (model QDR 4500 A, Hologic, Waltham, MA, USA and DPX-L OR DPX-IQ, Lunar Corp., Madison,
was scanned weekly to assess any machine drift over time. Although we recognize this to be a limitation of the study, there appears to be no significant difference in the reliability of the two systems (Diessel et al. 2000). For the AT and ST subjects, total body and hip scans were performed at baseline and again after the exercise training, using a standardized procedure for patient positioning. For the control subjects, total body and hip scans were performed before and after 16 weeks of no regular exercise. BMD was measured for the total body, greater trochanter, femoral neck and Wards triangle regions. We chose to focus on the femur because we found a significant increase in femoral neck BMD in previous studies but not in other regions (Menkes et al. 1993; Ryan et al. 1998), such as the vertebral bodies (Ryan et al. 1998). It is possible that this is because the leg press exercise requires moving the largest load and is the most proximal to the femoral neck. Total body fat-free mass (FFM), fat mass and percentage fat were also analysed. Total body FFM was defined as lean soft-tissue mass plus total body bone mineral content (BMC). The coefficients of variation (CV) for all DEXA measurements of body composition were calculated from repeated scans of 10 subjects who were scanned three consecutive times with repositioning. The CV was 0.6% for FFM and 1.0% for percentage fat. The scanner was calibrated daily against a spine calibration block and step phantom block supplied by the manufacturer. In addition, a whole body phantom was scanned weekly to assess any machine drift over time.

Body weight was determined to the nearest 0.1 kg with subjects dressed in medical scrubs, and height was measured to the nearest 0.1 cm using a stadiometer (Harpenden, Holtain, Wales, UK). BMI was calculated as weight (kg) divided by height squared (m²).

DNA genotyping

High-molecular weight genomic DNA was isolated from peripheral lymphocytes using standard methods. Subjects were genotyped for the VDR FokI and BsmI restriction site as previously described (Geusens et al. 1997; Zmuda et al. 1999). The VDR FokI genotype was defined as FF (absence of restriction site on both alleles), ff (presence of restriction site on both alleles), or Ff (heterozygotes). The VDR BsmI genotype was defined as BB (absence of restriction site on both alleles), bb (presence of restriction site on both alleles), or Bb (heterozygotes).

Statistical analyses

All statistical analyses were performed using SAS software (SAS version 8.1, SAS institute, Inc., Cary, NC, USA). ANOVA was conducted to determine differences in weight, BMI, percentage body fat and fat-free mass according to gender for both between and within groups. Differences in BMD at baseline between groups, gender and genotype were also determined by ANOVA.

We then used analysis of covariance (ANCOVA) to determine whether exercise training, regardless of modality, changed regional or total BMD in the entire study population, while covarying for age, gender, race and HRT status. If a change in regional or total BMD of the entire study population was detected, subsequent analyses were run to determine whether the change varied by age, gender or genotype. Between and within group (AT, ST and control) analyses were then performed. Planned comparisons were conducted using two-way repeated measures ANOVA to determine whether the effects of training were influenced by training modality or genotype. Two-way repeated measures ANCOVA was performed to determine the changes in BMD with exercise training. HRT, race, age and gender were used as covariates. The dependent variable in each ANCOVA was the change in BMD for each region of interest (femoral neck, greater trochanter, Wards triangle and total BMD). The independent variables included a gender term (men versus women), a genotype term (FF versus Ff versus ff) and a group term (AT versus ST versus control). Data are expressed as mean ± standard error of the mean (S.E.M.) and significance was set at P < 0.05.

Results

Group subject characteristics

At baseline there were no significant differences in weight, BMI, percentage body fat or fat-free mass within genders between the AT and ST groups (Table 1). In both the AT and ST groups, women had a higher percentage body fat and BMI, and a lower fat-free mass than men (P < 0.05). In the AT group, both men and women had a significant change in weight or BMI. There were no significant differences in baseline height, weight, BMI, percentage body fat and fat-free mass among groups. The independent variables included a gender term (men versus women), a genotype term (FF versus Ff versus ff) and a group term (AT versus ST versus control). Data are expressed as mean ± standard error of the mean (S.E.M.) and significance was set at P < 0.05.

There was a significant difference in age between the AT and ST groups (P < 0.05), with the mean age in the AT group being about 10 years younger than that of the ST group. In the AT group, percentage body fat, body weight and BMI changed significantly with training (P < 0.05, Table 1); whereas, percentage body fat decreased significantly (P < 0.05) and fat-free mass decreased significantly (P < 0.05) in the ST group.
increased significantly ($P < 0.05$) with training in the ST group. The control group did not change weight, percentage body fat, or fat-free mass over the study period.

### Bone mineral density

Baseline total body and regional BMD was significantly higher in the AT and control groups than the ST group (all $P < 0.05$, Table 2). Neither training modality resulted in a significant change in total or regional BMD measures. The BMD values after training appeared to move in the opposite direction in the ST group when compared to the AT and control groups, but these changes did not reach statistical significance (Table 2). There was no significant change in total or regional BMD between the two time points in the control group. Additionally, neither men nor women experienced a significant change in total or regional BMD.

### Genotype associations

To learn more about variation in response to training for each training programme, the influence of genotype at the VDR locus on response to training was assessed (Table 3). VDR FokI genotype was significantly related to training-induced changes in the femoral neck BMD in the ST group ($P < 0.05$), such that the Ff heterozygotes in the ST group approached a significantly greater increase in femoral neck BMD than ff homozygotes ($P = 0.058$). There was no significant influence of VDR FokI genotype on response to training in the AT group. Moreover, there were no significant influences of VDR FokI genotype and any baseline BMD measures (Table 3). VDR BsmI genotype was not significantly related to any baseline BMD or training-induced changes in total or regional BMD in either group.

### Discussion

To our knowledge, the present study is the first to compare exercise-training modalities for their effects on BMD and to demonstrate an association between VDR FokI genotype and BMD response to ST. No such relationship was found for response to AT. Our results indicate that VDR FokI may influence femoral neck BMD response to ST, with the heterozygotes having a greater ($P = 0.058$) femoral neck BMD response to ST than the f allele homozygotes (ff).

We are not aware of any other exercise-training studies that have investigated the VDR FokI genotype association with BMD response to training; however, others have studied the ff genotype and baseline femoral neck BMD (Gross et al. 1996; Harris et al. 1997). Some investigations have shown significant associations between the ff genotype at the VDR FokI locus and low BMD (Hannah & Norman, 1994; Gong et al. 1999) and between the FF genotype and high BMD (Gross et al. 1996; Arai et al. 1997; Harris et al. 1997; Ames et al. 1999; Kanan et al. 2000; Katsumata et al. 2002) in healthy populations.

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**Table 1. Physical characteristics before and after 6 months of aerobic and strength training**

<table>
<thead>
<tr>
<th></th>
<th>Aerobic training (n = 123)</th>
<th>Strength training (n = 83)</th>
<th>Control (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>Before: 57 ± 0.5</td>
<td>After: 67 ± 0.8</td>
<td>Before: 62 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>168 ± 0.9</td>
<td>167 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Wt (kg)</td>
<td>82.3 ± 1.1</td>
<td>76.6 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>28 ± 0.3</td>
<td>27 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Body fat (%)</td>
<td>37 ± 0.8</td>
<td>34 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>FFM (kg)</td>
<td>47.2 ± 1.0</td>
<td>48.1 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± s.e.m. BMI, body mass index (weight (kg)/height squared (m$^2$)); FFM, fat-free mass. *Significant difference, $P = 0.05$.

**Table 2. Bone mineral density (g cm$^{-2}$) before and after aerobic and strength training**

<table>
<thead>
<tr>
<th></th>
<th>Aerobic training (n = 123)</th>
<th>Strength training (n = 83)</th>
<th>Control (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before: 1.20 ± 0.01</td>
<td>After: 0.93 ± 0.01*</td>
<td>Before: 1.27 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>0.94 ± 0.01</td>
<td>0.79 ± 0.01*</td>
</tr>
<tr>
<td></td>
<td>Trochanter</td>
<td>0.85 ± 0.01</td>
<td>0.72 ± 0.02*</td>
</tr>
<tr>
<td></td>
<td>Wards triangle</td>
<td>0.80 ± 0.01</td>
<td>0.61 ± 0.02*</td>
</tr>
</tbody>
</table>

Values are means ± s.e.m. None of the differences between before and after training were significant in either group. *Significantly different ($P < 0.05$) from baseline (Before column) values for both Aerobic and Strength Training.

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Our results support the hypothesis by Nakamura et al. (2002) that variation in the VDR FokI gene may play an important role in explaining BMD variance in response to exercise training, rather than as a predictor of baseline BMD (Nakamura et al. 2002a). However, the mechanisms for this association are unknown. Nevertheless, these results do suggest that the conclusions made in previous investigations; that is, ST increases BMD (Snow-Harter et al. 1992; Menkes et al. 1993; Nelson et al. 1994; Ryan et al. 1994; Lohman et al. 1995), maintains (Pruitt et al. 1992; Ryan et al. 1995), decreases (Rockwell et al. 2000) or has no significant effect on BMD (Gleeson et al. 1990; Pruitt et al. 1992; Ryan et al. 2004), may be misleading. For example, without genotype data in this study, the conclusion would also be made that ST fails to increase regional or total BMD, but the genotype data could show that an increase in femoral neck BMD is associated with the Ff genotypes, but not ff genotypes at the VDR FokI gene locus.

We are not aware of any previous studies that have compared the effects of AT to ST on BMD. Current studies have either combined AT and ST or have addressed the effect of each separately. Studies that combine training modalities have produced disparate results (Rikli & McManis, 1990; Pruitt et al. 1992; Svendsen et al. 1993; Nelson et al. 1994; Ryan et al. 1994; Dalsky et al. 1998). A few studies that employ ST alone have shown no significant changes in BMD (Pruitt et al. 1992; Ryan et al. 1994; McCartney et al. 1995). Two studies from our laboratory showed significant increases in femoral neck BMD with ST, but used a very small sample size of subjects non-randomly assigned to training and control groups (Menkes et al. 1993; Ryan et al. 1994). Nelson et al. (1994) observed small increases in BMD after a 1-year, 2-days per week ST programme. However the changes in BMD were only

### Table 3. The influence of genotype on the change in total body, greater trochanter (GT), Wards triangle (WT) and femoral neck (FN) bone mineral density (BMD) after strength training (ST)

<table>
<thead>
<tr>
<th>VDR FokI (n = 64)</th>
<th>VDR BsmI (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td><strong>Change with ST</strong></td>
</tr>
<tr>
<td>FF 36</td>
<td>0.008 ± 0.004</td>
</tr>
<tr>
<td>Ff 21</td>
<td>−0.004 ± 0.016</td>
</tr>
<tr>
<td>ff 7</td>
<td>0.005 ± 0.008</td>
</tr>
<tr>
<td><strong>Greater trochanter</strong></td>
<td><strong>Change with ST</strong></td>
</tr>
<tr>
<td>FF 36</td>
<td>0.004 ± 0.004</td>
</tr>
<tr>
<td>Ff 21</td>
<td>0.001 ± 0.007</td>
</tr>
<tr>
<td>ff 7</td>
<td>−0.004 ± 0.010</td>
</tr>
<tr>
<td><strong>Femoral neck</strong></td>
<td></td>
</tr>
<tr>
<td>FF 36</td>
<td>0.002 ± 0.004</td>
</tr>
<tr>
<td>Ff 21</td>
<td>0.017 ± 0.008*</td>
</tr>
<tr>
<td>ff 7</td>
<td>−0.015 ± 0.011*</td>
</tr>
</tbody>
</table>

Values are means ± s.e.m. Ff genotype is significantly different from the ff genotype; *P = 0.05.

However, others have not confirmed either finding (Ames et al. 1999; Zmuda et al. 1999; Diesel et al. 2000). Cross-sectional investigations have shown differences in femoral neck BMD with different genotypes at the VDR FokI locus. For example, in a population of young Japanese men, Nakamura et al. (2002b) showed differences in BMD among competitive athletes engaged in weight-bearing activity compared to a non-athletic control group. They found that BMD was greater in the athletes with the FF genotype compared to controls, but there was no significant difference between athletes and controls among the athletes with Ff genotype (Nakamura et al. 2002b). This study by Nakamura and colleagues was limited by its cross-sectional design, a small sample size, the young age of the subjects and a low frequency of the ff genotype. Consequently, the Ff genotype group was not included in their analysis. In contrast, the present training study addresses the independent effects of ST in a larger sample size and in a population who are at an age in which losses in BMD are occurring (Kanis et al. 1994).

Gong et al. (1999) and Morrison et al. (1994) postulated that variation in the VDR FokI gene predicts individual differences in BMD. Arai et al. (1997) suggest that a T-to-C transition leads to a structural change in the VDR, which may lead to increased BMD (Arai et al. 1997; Colin et al. 2000; Jurutka et al. 2000; Whitfield et al. 2001). Our results support the hypothesis by Nakamura et al. (2002a) that variation in the VDR gene may determine the sensitivity of BMD response to environmental stimuli.

Moreover, the present study also supports their hypothesis that variation of the VDR FokI gene may play an important role in explaining BMD variance in response to exercise training, rather than as a predictor of baseline BMD (Nakamura et al. 2002a). However, the mechanisms for this association are unknown. Nevertheless, these results do suggest that the conclusions made in previous investigations; that is, ST increases BMD (Snow-Harter et al. 1992; Menkes et al. 1993; Nelson et al. 1994; Ryan et al. 1994; Lohman et al. 1995), maintains (Pruitt et al. 1992; Ryan et al. 1995), decreases (Rockwell et al. 2000) or has no significant effect on BMD (Gleeson et al. 1990; Pruitt et al. 1992; Ryan et al. 2004), may be misleading. For example, without genotype data in this study, the conclusion would also be made that ST fails to increase regional or total BMD, but the genotype data qualifies this conclusion by showing that an increase in femoral neck BMD is associated with the Ff genotypes, but not ff genotypes at the VDR FokI gene locus.

We are not aware of any previous studies that have compared the effects of AT to ST on BMD. Current studies have either combined AT and ST or have addressed the effect of each separately. Studies that combine training modalities have produced disparate results (Rikli & McManis, 1990; Pruitt et al. 1992; Svendsen et al. 1993; Nelson et al. 1994; Ryan et al. 1994; Dalsky et al. 1998). A few studies that employ ST alone have shown no significant changes in BMD (Pruitt et al. 1992; Ryan et al. 1994; McCartney et al. 1995). Two studies from our laboratory showed significant increases in femoral neck BMD with ST, but used a very small sample size of subjects non-randomly assigned to training and control groups (Menkes et al. 1993; Ryan et al. 1994). Nelson et al. (1994) observed small increases in BMD after a 1-year, 2-days per week ST programme. However the changes in BMD were only
significant when contrasted with the decrease in BMD in a sedentary control group. In comparison to the study of Nelson et al. (1994), the present study contains a much larger sample size, a shorter training period and a greater training frequency (3 days per week). Studies that have examined the effects of AT on BMD have also produced disparate results. Some have supported the findings in the present study that AT has no effect on BMD (Cavanaugh & Cann, 1988; Blumenthal et al. 1991; Prince et al. 1991; Bassey & Ramsdale, 1995; Ryan et al. 1998; Huuskonen et al. 2001), whereas others have demonstrated that AT can increase BMD (Kohrt et al. 1995; Dalsky et al. 1998). The reasons for these conflicting results are unclear, but it is probably due to differences in training mode, frequency, intensity and duration of exercise.

A limitation of the present study is that the BMD of the AT and ST groups was measured using DEXA machines manufactured by two different manufactures. This may explain the BMD difference between the AT and ST groups at baseline. However, as indicated at the end of the introduction, our purposes were to determine the influence of VDR FokI and BsmI genotypes on the independent effects of AT and ST on BMD and to compare the effectiveness of AT and ST for increasing BMD. Therefore, we are focusing on the change in BMD due to training and these two instruments do not appear to differ significantly in repeat BMD measurements (Diesell et al. 2000). A second limitation is the lack of an age-, gender- and genotype-matched sedentary control group. However, it would be difficult to obtain the ideal control group for this study because the primary research question focuses on the influence of genotype on BMD response to training. For this reason, the typical inactive control group would not control for normal variations within each genotype group. It would not be feasible or practical to recruit such a control group.

References


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