Journal of Osaka Kawasaki
Rehabilitation University Vol.*1, 2007.*
pp.*43-49*

総　説

Vitamin D receptor gene and exercise : influence on bone mineral density

Misa Nakamura*, Kyoko Minehisa, Seiji Togashi

Abstract : The population with osteoporosis is estimated at over ten million people in Japan. The consecutive increase of the case is therefore a serious problem in our aging society. Reducing the risk of bone fractures from osteoporosis involves preventing or delaying the loss of bone mineral density (BMD). BMD has been reported to be strongly determined genetically. The vitamin D receptor (VDR) is a good candidate gene for a prime regulator of BMD and bone metabolism. Many allelic variants in the VDR gene have been associated with BMD. In addition to the genetic background, exercise is also related to BMD. Recently, there is a growing realization that the physical response to a particular exercise stimulus may be mediated by individual genetic variability. This review briefly summarizes the influence of VDR polymorphism and exercise on BMD.

Key words; vitamin D receptor, exercise, bone mineral density, gene

Introduction

The prevalence of osteoporosis increases with age and reaches about 50% for women and 20% for men in their late seventies. In Japan, it is estimated that over 10 million people suffer from osteoporosis. Spine fracture is very common in the elderly, with a lifetime risk of 37% for a Japanese women aged 50. The incidence of spine fracture increases at relatively early stages of old age. Hip bone fracture rapidly increases among those aged over 70, with a lifetime risk of about 14% for women aged 50 and a 10-year fracture probability of 3% and 10% for women aged 70 and those aged 80, respectively[1].

Reducing the risk of bone fractures due to osteoporosis involves preventing or delaying the loss of bone mineral density (BMD). BMD is influenced by environment[2] and heredity[3) 4)]. Exercise has been recommended to retard age-related bone loss associated with osteoporosis[5]. Nevertheless, responses to exercise interventions are often highly variable among individuals. There is a growing realization that the physical response to a particular en-

* Misa Nakamura
Department of Physical Therapy, Faculty of Rehabilitation, School of Rehabilitation, Osaka Kawasaki Rehabilitation University,
E-mail: nakamuram@kawasakigakuen.ac.jp

vironmental stimulus, such as exercise, may be mediated by individual genetic variability[6]. The vitamin D receptor (VDR) gene has been targeted in research into the genetic determinants influencing bone status[7) 8)], because it regulates bone homeostasis through the vitamin D-endocrine system[9) 10)]. Furthermore, some epidemiological studies suggest that individual BMD is determined by the interaction between the physical activity level and variations in 3'-untranslated regions of the VDR[11)-13)].

The major focus of this review will be the effects of the VDR gene and exercise on bone metabolism.

Bone density and vitamin D receptor gene

BMD and bone turnover in adults are under genetic influence: in particular, serum osteocalcin concentration is strongly correlated with BMD and bone turnover in monozygotic twin pairs[14)]. The VDR gene has been targeted in BMD research[6) 7)] . The VDR gene is located on chromosome 12q[15)] and has several known allelic variants including a *BsmI* polymorphism in the intron between exons VIII and IX[16)] and *FokI* restriction length polymorphism in exon II[17)]. Most studies have focused on the *BsmI* polymorphism (allelic name 'B' for absence of the restriction site and 'b' for presence). The *BsmI* BB genotype has been associated with phenotype of a small to modest decrease in bone mass, and a 2-fold increase in the risk of hip bone 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 VIII and IX and 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 a functional polymorphism. This polymorphism, resulting in a C-to-T transition within exon II of the VDR gene, is defined by endonuclease *FokI* ('F' for the absence of the restriction site and 'f' for its presence) and creates an upstream initiation codon which leads to the production of receptor proteins that differ in length by three amino acids[5) 18) 19)]. A significant association of the FF genotype with phenotype of increased BMD has been reported in healthy populations[17) 19)-23)]. These results lead to the hypothesis that the shorter F allele may be more efficient in maintaining bone homeostasis[17) 19) 24)]. VDR *FokI* genotypes have been shown to influence BMD in the presence or absence of environmental stimuli[17) 19)-23)]. Gong et al. and Morrison et al.[7)] postulated that variation in the VDR *FokI* gene predicts individual differences in BMD. Arai *et al*[19) 24)-26)]. suggested that a C-to-T transition leads to a structural change in the VDR, which may lead to increased BMD.

Some investigations have shown significant associations between the ff genotype at the VDR *FokI* locus and low BMD[8) 9)] and between the FF genotype and high BMD[17) 19)-23)] in healthy populations. However, others have not confirmed either finding[22) 27) 28)].

Bone density and exercise

BMD is influenced by environment as much as by heredity. Mechanical load is one of the major environmental factors to influence BMD and bone metabolism[29]. Both aerobic training (AT) and strength training (ST) have been recommended to retard the age-related bone loss associated with osteoporosis. 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[30)-35)]. A few studies that employ ST alone have shown no significant changes in BMD[31) 32) 36)]. Nelson *et al.*[33] observed small increases in BMD after a 1-year, 2-days per week ST program. Two studies 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[34) 37)]. Studies that have examined the effects of AT on BMD have also produced disparate results. Some have reported that AT has no effect on BMD[38)-43)], whereas others have demonstrated that AT can increase BMD[35) 44)]. The reasons for these conflicting results are unclear, but it is probably due to differences in training mode, frequency, intensity and duration of exercise.

Effects of vitamin D receptor gene and exercise on bone density

Bray *et al.*[6] suggested that it is important to note that BMD response to exercise training may be influenced by inter-individual genetic variability. Tajima *et al.*[45] revealed differences in the response of bone metabolism to strenuous resistance exercise training in young Japanese men with different genotypes of the VDR detected by *FokI*. Despite a significant increase in 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) in the f group but not in the F group, the response of bone metabolism to training in the F group was similar to or greater than that in the f group. When the two training groups were analyzed separately, however, serum $1,25(OH)_2D_3$ concentration was increased by training in the f but not the F group. Thus the response of circulating $1,25(OH)_2D_3$ to resistance training is smaller in the F than in the f group. A similar response of bone formation to the training was observed, suggesting higher sensitivity of the F than the f VDR gene. The polymorphism, detected with *Fok* I, at the translation initiation site of the VDR gene results in a structural change that could potentially alter the function of the VDR protein. It has been reported that the longer allele of the VDR, designated f, may be less efficient in vitamin D-mediated transactivation in a transfected cell system[19) 46)], although significant differences in receptor function including ligand affinity of each genotype receptor have not been detected[20) 46)]. The physiological mechanism by which exercise training reveals functional difference in the two VDR variants remains to be clarified.

Some investigations have shown differences in bone phenotype with different genotypes at the VDR *FokI* locus. For example, in a population of young Japanese men (about[18)-21)] years old), Nakamura *et al.*[47] showed differ-

ences in BMD among competitive athletes engaged in weight-bearing sports with a high-impact load on their lower limbs (volley-ball, basketball, handball, and track-and field events such as the high jump and triple-jump) compared to a non-athletic control group. The increased spinal volume was found only in the athletes with the FF but not in those with the Ff genotype. Differences in bone mineral content in the lumbar spine and femoral neck between the controls and the athletes were greater in subjects with the FF rather than the Ff genotype[47].

Rabon-Stith *et al.*[48] investigated the effects of exercise on total body, greater trochanter and femoral neck BMD, measured before and after training 5-6 months (ST or AT program) in a population of old men and women (about 50-80 years old) living in the Washington, DC metropolitan area. The results showed that the VDR *BsmI* genotype was not significantly related to BMD at baseline or after ST or AT. However, the VDR *FokI* genotype was significantly related to ST- but not AT-induced changes in femoral neck BMD. Those participants with the Ff genotype in the ST group achieved a significantly greater increase in femoral neck BMD compared to the ff group. There were no significant genotype relationships in the AT group. These data indicate that the VDR *FokI* genotype may influence the femoral neck BMD response to ST, but not AT. These results support the hypotheses that variation in the VDR gene may determine the sensitivity of the BMD response to environmental stimuli. Moreover, these studies also support the hypothesis that variation of the VDR *FokI* gene may play an important role in explaining BMD variation in response to exercise training, rather than as a predictor of baseline BMD[49].

Nevertheless, these results do suggest that the conclusions drawn from previous investigations; that is, that ST increases BMD[33) 34) 37) 50) 51)], maintains[31)52)], decreases[53)] or has no significant effect on BMD[32) 54) 55)], may be misleading. For example, without consideration to genotype data, the conclusion would also be reached 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[48]. It must, therefore, be emphasized that the inter-individual allelic variation of genes is very important part.

Future directions

The factors involved in human physiology and health are extremely complex. It must, therefore, be emphasized that the inter-individual allelic variation of genes can play an important part. Genotype 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-environmental interaction.

However, the mechanisms involved in this association are unknown. Understanding the cellular, biochemical, and molecular basis of gene-exercise interactions using animal model is essential to improving human BMD and preventing osteoporosis through exercise.

[References]

1) Fujiwara S Epidemiology of osteoporosis and fracture Clin Calcium. 2004 14(11): 13-18.
2) Ziegler R, Scheidt-Nave C, Scharla S Pathophysiology of osteoporosis: unresolved problems and new insights. J Nutr. 1995; 125: 2033S-2037S.
3) Smith DM, Nance WE, Kang KW, Christian JC, Johnston CC Jr Genetic factors in deter-mining bone mass. J Clin Invest. 1973; 52: 2800-2808
4) Rodan GA, Fleisch HA Bisphosphonates: mechanisms of action. J Clin Invest. 1996 15; 97: 2692-2696.
5) Saijo T, Ito M, Takeda E, Huq AH, Naito E, Yokota I, Sone T, Pike JW, Kuroda Y A unique mutation in the vitamin D receptor gene in three Japanese patients with vitamin D-dependent rickets type II: utility of single-strand conformation polymorphism analysis for heterozygous carrier detection. Am J Hum Genet. 1991; 49: 668-673.
6) Bray MS Genomics, genes, and environmental interaction: the role of exercise. J Appl Phy-siol. 2000; 88: 787-792.
7) Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN, Eisman JA Prediction of bone density from vitamin D receptor alleles. Nature. 1994; 367: 284-287.
8) Gong G, Stern HS, Cheng SC, Fong N, Mordeson J, Deng HW, Recker RR The associ-ation of bone mineral density with vitamin D receptor gene polymorphisms. Osteoporos Int. 1999; 9: 55-64.
9) Hannah SS, Norman AW 1 alpha, 25 (OH) 2 vitamin D3-regulated expression of the eukaryotic genome. Nutr Rev. 1994; 52: 376-382.
10) Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Thompson PD, Selznick SH, Dominguez CE, Jurutka PW The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. J Bone Miner Res. 1998; 13: 325-349.
11) Salamone LM, Ferrell R, Black DM, Palermo L, Epstein RS, Petro N, Steadman N, Kuller LH, Cauley JA The association between vitamin D receptor gene polymorphisms and bone mineral density at the spine, hip and whole-body in premenopausal women. Osteoporos Int. 1996; 6(1): 63-68.
12) Rubin LA, Hawker GA, Peltekova VD, Fielding LJ, Ridout R, Cole DE Determinants of peak bone mass: clinical and genetic analyses in a young female Canadian cohort. J Bone Miner Res. 1999; 14(4): 633-643.
13) Blanchet C, Giguere Y, Prud'homme D, Dumont M, Rousseau F, Dodin S Association of physical activity and bone: influence of vitamin D receptor genotype. Med Sci Sports Exerc. 2002; 34: 24-31.
14) Kelly PJ, Hopper JL, Macaskill GT, Pocock NA, Sambrook PN, Eisman JA Genetic factors in bone turnover. J Clin Endocrinol Metab. 1991; 72: 808-813.
15) Szpirer J, Szpirer C, Riviere M, Levan G, Marynen P, Cassiman JJ, Wiese R, DeLuca HF The Sp1 transcription factor gene (SP1) and the 1,25-dihydroxyvitamin D(3) receptor gene (VDR) are colocalized on human chromosome arm 12q and rat chromosome 7. Genomics. 1991; 11: 168-173.
16) Morrison NA, Yeoman R, Kelly PJ, Eisman JA Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci USA. 1992; 89: 6665-6669.
17) Gross C, Eccleshall TR, Malloy PJ, Villa ML, Marcus R, Feldman D The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postme-nopausal Mexican-American women. J Bone Miner Res. 1996; 11: 1850-1855.
18) Gross C, Krishnan AV, Malloy PJ, Eccleshall TR, Zhao XY, Feldman D The vitamin D receptor gene start codon polymorphism: a functional analysis of FokI variants. J Bone Miner Res. 1998; 13: 1691-1699.
19) Arai H, Miyamoto K, Taketani Y, Yamamoto H, Iemori Y, Morita K, Tonai T, Nishisho T, Mori S, Takeda E A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women. J Bone Miner Res. 1997; 12: 915-921.
20) Katsumata K, Nishizawa K, Unno A, Fujita Y, Tokita A Association of gene polymorp-hisms

and bone density in Japanese girls. J Bone Miner Metab. 2002; 20: 164-169.

21) Harris SS, Eccleshall TR, Gross C, Dawson-Hughes B, Feldman D The vitamin D receptor start codon polymorphism (FOK I) and bone mineral density in premenopausal American black and white women. J Bone Miner Res. 1997; 12: 1043-1048.

22) Ames SK, Ellis KJ, Gunn SK, Copeland KC, Abrams SA Vitamin D receptor gene Fok I polymorphism predicts calcium absorption and bone mineral density in children. J Bone Miner Res. 1999; 14: 740-746.

23) Kanan RM, Varanasi SS, Francis RM, Parker L, Datta HK Vitamin D receptor gene start codon polymorphism (Fok I) and bone mineral density in healthy male subjects. Clin Endocrinol (Oxf). 2000; 53: 93-98.

24) Colin EM, Weel AE, Uitterlinden AG, Buurman CJ, Birkenhager JC, Pols HA, van Leeuwen JP Consequences of vitamin D receptor gene polymorphisms for growth inhibition of cultured human peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D3. Clin Endocrinol (Oxf). 2000; 52: 211-216.

25) Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, Tavakkoli P, Galligan MA, Dang HT, Haussler CA, Haussler MR The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. Mol Endocrinol. 2000; 14: 401-420.

26) Whitfield GK, Remus LS, Jurutka PW, Zitzer H, Oza AK, Dang HT, Haussler CA, Galligan MA, Thatcher ML, Encinas Dominguez C, Haussler MR Functionally relevant polymorp-hisms in human nuclear vitamin D receptor gene. Mol Cell Endocrinol. 2001; 177: 145-159.

27) Zmuda JM, Cauley JA, Danielson ME, Theobald TM, Ferrell RE Vitamin D receptor translation initiation codon polymorphism and makers of osteoporotic risk in older African-American women. Osteoporos Int. 1999; 9: 214-219.

28) Diessel E, Shepherd J, Fuerst T, Gonzalez M, Genant HK, Carew B, Looker A Comparison of two phantoms for body composition with dual-energy x-ray absorptiometry. Ann NY Acad Sci. 2000; 904: 107-110.

29) Frost, HM Proposed general concepts for skeletal adaptations to mechanical usage. Calcif Tissue Int. 1988; 42: 145-156.

30) Rikli RE & McManis BG Effects of exercise on bone mineral content in postmenopausal women. Res Q Exerc Sport. 1990; 613: 243-249.

31) Pruitt LA, Jackson RD, Bartels RL, Lehnhard HJ Weight training effects bone mineral density in early postmenopausal women. J Bone Miner Res. 1992; 7: 179-185.

32) Svendsen OL, Hassager C, Christiansen C Effect of an energy-resistive diet, with or without exercise, on lean tissue mass, resting metabolic rate, cardiovascular risk factors, and bone in overweight postmenopausal women. Am J Med. 1993; 95: 131-140.

33) Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures: a randomized controlled trial. JAMA. 1994; 272: 1909- 1914.

34) Ryan AS, Treuth MS, Rubin MA, Miller JP, Nicklas BJ, Landis DM, Pratley RE,Libanati CR, Gundberg CM, Hurley BF Effects of strength training on bone mineral density: hormonal and bone turnover relationships. J Appl Physiol. 1994; 77: 1678-1684.

35) Dalsky GP, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birge SJ Jr Weight- bearing exercise training and lumbar bone mineral content in postmenopausal women. Ann Intern Med. 1998; 108: 824-828.

36) McCartney N, Hicks AL, Martin J, Webber CE Long-term resistance training in the elderly: effects on dynamic strength, exercise capacity, muscle, and bone. J Gerontol A Biol Sci Med Sci. 1995; 50: B97-104.

37) Menkes A, Mazel S, Redmond R Strength training increases regional bone mineral density and bone remodeling in middle-age and older men. J Appl Physiol. 1993; 74: 2478-2484.

38) Cavanaugh DJ, Cann CE Brisk walking does not stop bone loss in postmenopausal women. Bone. 1988; 9: 201-204.

39) Blumenthal JA, Emery CF, Madden DJ, Schniebolk S, Riddle MW, Cobb FR, Higgin-

botham M, Coleman RE Effects of exercise training on bone density in older men and women. J Am Geriatr Soc. 1991; 39: 1065-1070.

40) Prince RL, Smith M, Dick IM, Price RI, Webb PG, Henderson NK, Harris MM Prevention of postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation, and hormone- replacement therapy. N Engl J Med. 1991; 325: 1189-1195.

41) Bassey EJ, Ramsdale SJ Weight-bearing exercise and ground reaction forces: a 12-month randomized controlled trail of effects on bone mineral density in healthy postmenopausal women. Bone. 1995; 16: 469-479.

42) Ryan AS, Nicklas B, Dennis KE Aerobic exercise maintains regional bone mineral density during weight loss in postmenopausal women. J Appl Physiol. 1998; 84: 1305-1310.

43) Huuskonen J, Vaisanen SB, Kroger H, Jurvelin JS, Alhava E, Rauramaa R Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. Osteoporos Int. 2001; 12: 349-355.

44) Kohrt WM, Snead DB, Slatopolsky E, Birge SJ Jr Additive effects of weight- bearing exercise and estrogen on bone mineral density in older women. J Bone Miner Res. 1995; 10: 1303-1311.

45) Tajima O, Ashizawa N, Ishii T, Amagai H, Mashimo T, Liu LJ, Saitoh S, Tokuyama K, Suzuki M. Interaction of the effects between vitamin D receptor polymorphism and exercise training on bone metabolism. J Appl Physiol. 2000; 88: 1271-1276.

46) Miyamoto K, Taketani Y, Arai H A novel polymorphism in the vitamin D receptor gene and bone mineral density: study of vitamin D receptor expression and function in COS-7 cells. J Bone Miner Res. 1996; 11: S116.

47) Nakamura O, Ishii T, Mankyu H, Tsubakimoto S, Nomura T, Tokuyama K Contribution of vitamin D receptor genotypes to bone mineral density in young male athletes with different impact loading. Eur J Sport Sci. 2002; 2: 1-8.

48) Rabon-Stith KM, Hagberg JM, Phares DA, Kostek MC, Delmonico MJ, Roth SM, Ferrell RE, Conway JM, Ryan AS, Hurley BF. Vitamin D receptor FokI genotype influences bone mineral density response to strength training, but not aerobic training. Exp Physiol. 2005; 90: 653- 661.

49) Nakamura O, Ishii T, Ando Y, Amagai H, Oto M, Imafuji T, Tokuyama K Potential role of vitamin D receptor gene polymorphism in determining bone phenotype in young male athletes. J Appl Physiol. 2002; 93: 1973-1979.

50) Snow-Harter C, Whalen R, Myburgh K, Arnaud S, Marcus R Bone mineral density, muscle strength, and recreational exercise in men. J Bone Miner Res. 1992; 7: 1291-1296.

51) Lohman T, Going S, Pamenter R, Hall M, Boyden T, Houtkooper L, Ritenbaugh C, Bare L, Hill A, Aickin M Effects of resistance and endurance exercise on bone mineral density in premenopausal women: a randomized prospective study. J Bone Miner Res. 1995; 10: 1015-1024.

52) Ryan AS, Prately RE, Elahi D Resistive training increases fat-free mass and maintains RMR despite weight loss in postmenopausal women. J Appl Physiol. 1995; 79: 818-823.

53) Rockwell JC, Sorensen AM, Baker S, Leahey D, Stock JL, Michaels J, Baran DT Weight training decreases vertebral bone density in premenopausal women: a prospective study. Br J Sports Med. 2000; 34: 18-22.

54) Gleeson PB, Protas EJ, LeBlanc AD, Schneider VS, Evans HJ Effects of weight lifting on bone mineral density in premenopausal women. J Bone Miner Res. 1990; 5: 153-158.

55) Ryan AS, Ivey FM, Hurlbut DE, Martel GF, Lemmer JT, Sorkin JD, Metter EJ, Fleg JL, Hurley BF Regional bone mineral density after resistive training in young and older men and women. Scand J Med Sci Sports. 2004; 14: 16-23.