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Association of *APOE* Genotype with Bone Mineral Density in Men and Women: The Dong-gu and Namwon Studies

Sun A Kim[1], Sun-Seog Kweon[1], Jin-Su Choi[1], Jung-Ae Rhee[1], Young-Hoon Lee[2], Hae-Sung Nam[3], Seul-Ki Jeong[4], Kyeong-Soo Park[5], So-Yeon Ryu[6], Seong-Woo Choi[6], Hee Nam Kim[7], Hye-Rim Song[8], Su-hyun Oh[1], Jane A. Cauley[9] and Min-Ho Shin[1,7,*]

[1]Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, [2]Department of Preventive Medicine & Institute of Wonkwang Medical Science Wonkwang University College of Medicine, Iksan, [3]Department of Preventive Medicine, Chungnam National University Medical School, Daejeon, [4]Department of Neurology & Research Institute of Clinical Medicine, Chobuk National University-Chonbuk National University Hospital, Jeonju, [5]Department of Preventive Medicine, Seonam University College of Medicine, Namwon, [6]Department of Preventive Medicine, Chosun University Medical School, Gwangju, [7]Center for Creative Biomedical Scientists, Chonnam National University, Gwangju, [8]Department of Laboratory Medicine, Chonnam National University Hwasun Hospital, Hwasun, Korea, [9]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, USA

Many studies have investigated relationships between *APOE* genotype and bone mineral density (BMD). However, the results of these studies have been inconsistent. Few studies have been carried out in Asian populations. We studied the relationship of the *APOE* gene polymorphism and BMD in two large population-based studies. The datasets included the Dong-gu Study (3575 men and 5335 women) and the Namwon Study (2310 men, 3512 women). Lumbar spine and femoral neck BMD were measured by dual-energy X-ray absorptiometry. *APOE* genotypes were analyzed by polymerase chain reaction–restriction fragment length polymorphism. The *APOE* genotypes were classified into *APOE E2* (*E2/E2* and *E2/E3*), *APOE E3* (*E3/E3*), and *APOE E4* (*E3/E4* and *E4/E4*). The genotype distribution of the study population was in Hardy-Weinberg equilibrium. There were no significant differences among *APOE* genotype groups in lumbar and femoral neck BMD in either cohort. Our data do not support the hypothesis that the *APOE* genotype is associated with BMD.

Key Words: *Apolipoprotein E; Polymorphism, genetic; Bone density*

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Corresponding Author:
Min-Ho Shin
Department of Preventive Medicine, Chonnam National University Medical School, 160, Baekseo-ro, Dong-gu, Gwangju 61469, Korea
TEL: +82-62-220-4166
FAX: +82-62-233-0305
E-mail: mhshinx@paran.com

INTRODUCTION

Apolipoprotein E (*APOE*) is a plasma protein with a central role in the metabolism of cholesterol and triglycerides by binding to receptors on the liver to help mediate clearance of triglyceride-rich lipoproteins from the plasma.[1,2] The *APOE* gene has three common alleles (*E2, E3*, and *E4*) that arise from two single-nucleotide polymorphisms in exon 4 that give six possible genotypes (*E2/E2*, *E2/E3*, *E2/E4*, *E3/E3*, *E3/E4*, and *E4/E4*).[3]

The *APOE* gene has been established as a novel regulator of bone metabolism in mice, in which *APOE* deficiency leads to a high bone mass phenotype.[4] In addition, the *APOE* gene has been associated with various diseases such as dyslipidemia, atherosclerosis, and neurodegenerative disease, which often coexist with osteoporosis. In our previous report using the same cohorts of this study, we showed that the *APOE* genotype is associated with carotid atherosclerosis.[5]

Since Shiraki and colleagues first described the association of the *APOE E4* allele with low bone mineral density (BMD) in 1997,[6] many studies have investigated relationships between *APOE* genotype and BMD. However, the results of these studies have been inconsistent. A meta-analysis does not support a consistent association of the *APOE E4* allele with BMD or fracture risk.[7] Moreover, most previous studies included a limited number of subjects (less than 1,000 subjects in most cases) and were carried out in Caucasians. Few studies have been carried out in Asians. Therefore, we examined cross-sectional associations be-

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tween *APOE* genotype and BMD in two large, independent cohorts from South Korea: the Dong-gu Study and the Namwon Study.

MATERIALS AND METHODS

1. Subjects

The Dong-gu Study and the Namwon Study are prospective studies designed to investigate the risk factors for chronic disease in urban and rural populations, respectively. The study protocols have been published previously.[8]

The Dong-gu Study enrolled 9,260 subjects aged 50 years and older from 2007 to 2010 in the Dong-gu district of Gwangju Metropolitan City in South Korea. Of those, 9,206 subjects underwent BMD measurement using a Lunar Prodigy bone densitometer (GE, Madison, WI, USA), and BMD data for both the lumbar spine and femoral neck were available for 9,056 subjects. *APOE* genotype and lipid data were available for 9,029 participants. A total of 119 subjects with the *APOE E2/E4* genotype were excluded. The final sample consisted of 8,910 individuals (3,575 men and 5,335 women).

The Namwon Study enrolled 10,667 subjects (4,201 men and 6,466 women) aged 45 to 74 years from 2004 to 2007 in Namwon city of Jeollabuk-do province in South Korea. A total of 6,135 subjects underwent BMD measurement with a Lunar Prodigy bone densitometer (GE, Madison, WI, USA), and BMD data for the lumbar spine and femoral neck were available for 5,954 subjects. APOE genotype and lipid data were available for 5,892 participants. Seventy subjects with the *APOE E2/E4* genotype were excluded. The final sample consisted of 5,822 individuals (2,310 men, 3,512 women).

These two studies were approved by the institutional review board of Chonnam National University Hospital (the Dong-gu Study, IRB No. I-2008-05-056; the Namwon Study, IRB No. I-2007-07-062), and written informed consent was obtained from all subjects.

2. Determination of bone mineral density

Lumbar spine and femoral neck BMD were measured by dual-energy X-ray absorptiometry (Lunar Prodigy; GE, Madison, WI, USA). Lumbar spine BMD represents the average BMD of the L1 to L4 vertebrae. A phantom was scanned daily for proper quality control. All BMD scans were conducted by using standardized procedures following the manufacturer's recommended protocols by well-trained examiners. Intra-scanner reproducibility, expressed as the coefficient of variation, was less than 1%. One experienced investigator reviewed all scans and unacceptable scans were reanalyzed. Lumbar spine scans with insufficient scanning of L1 or L4, metal implants, severe degenerative changes, or compression fractures were excluded.

3. Genotyping

Genomic DNA was extracted from peripheral blood by use of commercial DNA extraction kits (AccuPrep Genomic DNA Extraction Kit, Bioneer, Seoul, Korea, or a QIAamp DNA Mini Kit, Qiagen Inc., Chatsworth, CA, USA) according to the manufacturer's protocol. *APOE* genotypes were determined as described by Hixson and Vernier, with slight modification.[9,10]

4. Other measurements

Weight was measured to the nearest 0.1 kg with the subjects in light clothing. Height was measured to the nearest 0.1 cm without shoes. Venous blood was collected from subjects after they had fasted overnight. Serum was separated and stored at $-70^{\circ}C$ until assayed. Serum lipids (cholesterol, HDL cholesterol, and triglycerides) were measured by use of enzyme methods. Smoking status was categorized as ever or never smoker.

5. Statistical analysis

The *APOE* genotypes were classified into *APOE E2* (*E2/E2* and *E2/E3*), *APOE E3* (*E3/E3*), and *APOE E4* (*E3/E4* and *E4/E4*). Subjects with the *E2/E4* genotype were excluded because they carry both alleles. Data are presented as means±standard deviations for continuous variables or as numbers and percentage for categorical variables. Differences in baseline characteristics among *APOE* genotypes were compared by using the chi-square, one-way ANOVA, or Kruskal-Wallis test as appropriate. All analyses were stratified by sex, and multiple linear regression analysis was performed to evaluate the association between *APOE* genotypes and spine and femoral neck BMD, adjusting for age, height, weight, smoking status, total cholesterol, HDL cholesterol, and log-transformed triglycerides. Hardy-Weinberg equilibrium was tested by chi- square test. Statistical analyses were performed by using SPSS software version 20.0 (IBM SPSS, Chicago, IL, USA). Statistical significance was defined at $p < 0.05$.

RESULTS

The *APOE* genotype distribution was in accordance with Hardy-Weinberg equilibrium (p=0.89 for the Dong-gu Study, p=0.77 for the Namwon Study, respectively) and did not differ significantly between the two cohorts. *APOE* genotype frequency for *E2/E2, E2/E3, E2/E4, E3/E3, E3/E4*, and *E4/E4* was 0.4%, 10.7%, 1.3%, 71.1%, 15.5%, and 0.9%, respectively in the Dong-gu Study and 0.3%, 9.6%, 1.2%, 73.2%, 14.9%, and 0.8%, respectively in the Namwon Study.

The characteristics of both study cohorts according to *APOE* genotype group are presented in Table 1. The overall mean age of the Namwon cohort (61.2±8.1 years) was lower than that of the Dong-gu cohort (65.1±8.2 years). In each cohort and sex group, total cholesterol in the *APOE E2* group was lower than in the *APOE E3* and *APOE E4* groups and HDL cholesterol in the *APOE E4* group was lower than in the *APOE E2* and *APOE E3* groups. Triglycerides were significantly lower in the *APOE E3* group than in the *APOE E2* and *APOE E4* groups in each cohort except for men in

TABLE 1. Characteristics of the study subjects according to *APOE* genotype group

	Men				Women			
	E2	*E3*	*E4*	p value	*E2*	*E3*	*E4*	p value
Dong-gu study								
N	419	2,553	603		587	3,868	880	
Age (years)	66.1±7.7	66.3±8	66.0±8.3	0.72	63.9±8.2	64.5±8.3	64.5±7.8	0.224
Height (cm)	165.9±5.6	165.9±5.8	165.6±5.5	0.428	153.3±5.6	153.2±5.5	153±5.5	0.475
Weight (kg)	65.2±9.1	66.2±9.1	65.2±9.5	0.010	58.2±7.7	57.9±8.0	57.5±7.9	0.320
Ever smoker	305 (72.8)	1,885 (73.8)	447 (74.1)	0.881	16 (2.7)	142 (3.7)	32 (3.6)	0.511
Total cholesterol (mg/dL)	178.8±34.3	191.8±38.2	191.8±38.4	<0.001	196.1±40.6	210.2±38.8	210.9±40	<0.001
HDL cholesterol (mg/dL)	50.6±11.9	49.9±11.9	47.9±11.5	<0.001	54.2±12.2	53.1±11.7	51.4±11.5	<0.001
Triglycerides (mg/dL)	151.7±109.8	144.1±115.7	148.9±97.7	0.021	154.3±132.8	136.4±83.0	150.2±96.3	<0.001
Namwon study								
N	230	1,704	376		354	2,607	551	
Age (years)	61.8±8.1	61.9±7.9	61.6±7.6	0.717	60.3±8.2	60.8±8.2	60.7±8.4	0.595
Height (cm)	164.7±5.8	164.9±5.9	165.1±6	0.694	152.4±5.3	152±5.5	151.9±5.7	0.299
Weight (kg)	65.2±9.3	65.6±9.5	66.0±9.1	0.573	56.7±8.4	56.8±8.4	56.8±8.8	0.981
Ever smoker	188 (81.7)	1,346 (79.0)	287 (76.3)	0.272	21 (5.9)	128 (4.9)	24 (4.4)	0.563
Total cholesterol (mg/dL)	169.6±35.3	182.4±34.6	184.6±34.1	<0.001	179.1±35.9	194.6±36	197.7±35.9	<0.001
HDL cholesterol (mg/dL)	46.2±12.0	45.8±11.0	44.0±10.6	0.010	49.8±12.6	48.3±11.2	46.3±10.5	<0.001
Triglycerides (mg/dL)	180.6.±152.2	163.2±121.2	175.9±147.9	0.056	159.5±112.4	147.0±91.2	165.4±112.1	0.001

Data are mean±standard deviation or number (percentage). HDL: high-density lipoprotein. p-values were determined by ANOVA or Pearson's chi-square test as appropriate; for triglycerides, Kruskal-Wallis rank test was used.

TABLE 2. Difference in bone mineral density (g/cm^2) by *APOE* genotype group

	Men				Women			
	E2	*E3*	*E4*	p value	*E2*	*E3*	*E4*	p value
Dong-gu study								
Lumbar spine								
Model 1	1.162±0.009	1.163±0.004	1.146±0.008	0.150	0.985±0.006	0.984±0.002	0.986±0.005	0.940
Model 2	1.161±0.009	1.163±0.004	1.147±0.008	0.172	0.983±0.006	0.984±0.002	0.986±0.005	0.932
Femoral neck								
Model 1	0.883±0.006	0.880±0.002	0.880±0.005	0.875	0.783±0.004	0.788±0.002	0.787±0.003	0.541
Mode 2	0.884±0.006	0.880±0.002	0.881±0.005	0.852	0.783±0.004	0.788±0.002	0.787±0.003	0.552
Namwon study								
Lumbar spine								
Model 1	1.134±0.011	1.119±0.004	1.119±0.009	0.461	0.986±0.008	0.972±0.003	0.971±0.006	0.209
Mode 2	1.133±0.011	1.120±0.004	1.118±0.009	0.506	0.978±0.008	0.972±0.003	0.975±0.006	0.755
Femoral neck								
Model 1	0.902±0.007	0.891±0.003	0.900±0.006	0.196	0.823±0.005	0.818±0.002	0.817±0.004	0.612
Mode 2	0.904±0.007	0.891±0.003	0.899±0.006	0.187	0.823±0.005	0.818±0.002	0.817±0.004	0.611

Data are presented as mean±standard error. Model 1: adjusted for age, weight, and height. Model 2: adjusted for age, weight, height, smoking status, total cholesterol, HDL cholesterol, and log-transformed triglycerides.

the Namwon cohort. Weight was higher in the *APOE E3* group than in the *APOE E2* and *APOE E4* groups in men of the Dong-gu cohort. No other statistically significant differences were observed.

There was no evidence that BMD varied by *APOE* genotype group. This was true for both the lumbar spine and femoral neck in men and women in both cohorts (Table 2). Adjustment for age, height, weight, and blood lipids did not significantly influence these results.

DISCUSSION

In this large cross-sectional study, we found no association between APOE gene polymorphism and BMD in men or women. To our knowledge, this is the largest study to date regarding the association between the *APOE* gene polymorphism and BMD in Asians.

Several studies have reported cross-sectional and longitudinal associations between *APOE E4* and BMD in the

general population.[6,11-14] In 1997, Shiraki et al.[6] first reported that BMD values were significantly reduced in *APOE E4* carriers among 284 Japanese postmenopausal women. In the Longitudinal Aging Study Amsterdam of 519 participants (≥65 years), Pluijm et al.[13] found that *APOE E4* was associated with significantly lower femoral neck and trochanter BMD in women and was associated with hip BMD only in the 65–69-year-old age group in men. In an Australian study of 940 postmenopausal women (≥ 70 years), Dick et al.[14] found an association of *APOE E4* with hip BMD. Interestingly, in a longitudinal study of 392 pre-, peri-, and postmenopausal women, Salamone et al.[11] found no significant differences in baseline BMD at the spine or hip when comparing women with and without *APOE E4*, but found that women having *APOE E4* experienced significant bone loss over 2.5 years of follow-up compared with women without this allele. In addition, in a Korean study of 110 women with rheumatoid arthritis, Lee et al.[15] reported a significant association of the *APOE E4* allele with lumbar spine and femoral greater trochanter BMD. All of the studies reporting this association had sample sizes of less than 1,000. However, other studies including two large cohort studies have reported that there is no association between *APOE E4* and BMD,[16-20] which is in line with our results. In the Rotterdam Study of 5,386 participants aged 55 years and older,[20] there were no associations of the *APOE E4* allele with BMD, rate of bone loss, or fracture risk. In particular, a recent meta-analysis of 17 published observational studies[7] did not support the association of *APOE E4* genotype with BMD or with fracture risk. Three recent genome-wide association studies[21-23] also did not detect any variants in or near the *APOE* gene for BMD.

It may be hypothesized that *APOE E2* confers protection on BMD because of differential effects of the *E2* an *E4* isoforms on lipid metabolism.[4] However, because most studies have only compared carriers of *APOE E4* with noncarriers of *APOE E4*, few studies have addressed the specific effects of *APOE E2*.[4,24] In a longitudinal study of 2,659 women aged 45 to 54 years, Macdonald et al.[25] found that lumbar spine and femoral neck BMD were greater in carriers of the *E2* allele than in carriers of the *E4* allele, and there was less bone loss for carriers of the *E2* allele in the lumbar spine and femoral neck. However, in our study, we did not find the putative protective effect of *APOE E2*. Our results are in line with two previous studies.[19,24] Stulc et al.[19] found no significant differences in lumbar spine, proximal femur, or distal forearm BMD between subjects with the *APOE E2/E2* (n=7) and *APOE E4/E4* (n=11) genotype out of 873 dyslipidemic patients. Gerdes et al.[24] found no differences between six *APOE* genotypes in baseline BMD in five different regions of the skeleton and total body in 479 perimenopausal Danish women aged 45-58 years.

There are several possible mechanisms underlying a link between *APOE* polymorphism and BMD. It is suggested that because of the higher affinity of *APOE E4* for lipoprotein receptors, *APOE E4* carriers have lower plasma levels of vitamin K, which is essential for the biosynthesis of osteocalcin, an important bone protein.[26] Another hypothesis is that *APOE E4* may be linked to BMD through increased low-density lipoprotein levels and that oxidized lipid accumulation in the subendothelial matrix of bone may inhibit osteoblast differentiation.[27,28]

This study had several limitations. First, we did not evaluate associations between *APOE* genotype and fractures. Second, noncoding regions of the *APOE* gene may influence BMD.[29,30] However, we did not genotype other loci. Third, *APOE* can influence BMD by gene-environment interaction rather than by direct genetic effects. However, we did not evaluate gene-environment interaction. Fourth, we evaluated associations between *APOE* genotype and BMD in adults aged 50 years and older. *APOE* may influence the development of peak BMD by modulating the rate of bone loss with age.

In conclusion, we found no association between *APOE* genotype and BMD in two large cohorts from South Korea. Although we cannot rule out the possibility that the *APOE* gene may influence BMD through gene-gene or gene-environment interactions, our results suggest that the *APOE* genotype does not impact BMD, at least in a Korean population, which is consistent with observations in Caucasians.

CONFLICT OF INTEREST STATEMENT

None declared.

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