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ApoE Polymorphism May Determine Low-Density Lipoprotein Cholesterol Level in Association with Obesity and Metabolic Syndrome in Postmenopausal Korean Women

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Purpose: We investigated how serum low-density lipoprotein (LDL) level is related to various isoforms of apolipoprotein (ApoE) polymorphism in association with obesity and metabolic syndrome. **Materials and Methods:** We gathered total 332 sample of postmenopausal Korean women and analyzed ApoE isoforms, serum lipid level including LDL, blood pressure, fasting glucose, and anthropometry. The relationship between ApoE isoforms and serum lipid level, metabolic syndrome, and obesity was investigated. **Results:** Six ApoE isoforms were found, ApoE2 [E2/2 (n=1), E2/3 (n=54), E2/4 (n=14)], ApoE3 (E3/3, n=200), ApoE4 [E3/4 (n=55), and E4/4 (n=8)]. The prevalence of metabolic syndrome and obesity showed higher ApoE3 isoform than that of other isoforms. In additon, ApoE3 isoform was related to higher serum LDL and total cholesterol level than to ApoE2 isoform. The odds ratio of having the highest LDL cholesterol quartile in ApoE3 with obesity, compared to ApoE2 without obesity, was 3.46 [95% confidence interval (CI); 1.07-11.14, p=0.037], and odds ratio of ApoE3 with metabolic syndrome compared to ApoE2 without metabolic syndrome was 5.06 (95% CI; 1.14-22.29, p=0.037). Serum LDL cholesterol was positively associated with obesity or metabolic syndrome in ApoE3 isoform. **Conclusion:** This study suggests that obesity or metabolic syndrome risk should be effectively managed in ApoE3 isomform groups to reduce serum LDL in postmenopausal Korean women.

Key Words: ApoE polymorphism, LDL, obesity, metabolic syndrome

INTRODUCTION

Apolipoprotein E (ApoE) is a 34 kDa protein that plays an important role in lipoprotein metabolism by association with lipoprotein particles and with members of the low-density lipoprotein (LDL) receptor family.[1,2] It has been known that there are three apoE isoforms, E2, E3 and E4, have different affinities for their binding receptors. In case of apoE2, defective characteristics of binding to low density lipoprotein receptor (LDLR) by cysteine at amino acid position 158,[3] which affects up-regulation of synthesis of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and LDLR and finally results in low serum LDL level. Therefore, even

though those with the allele epsilon2 have a (low) risk for the rare form of hyperlipidemia (type III),[4] they actually have relatively low LDL-C. In contrast, E4 has a characteristic of rapid clearance and down-regulation of both HMA-CoA and LDLR, which causes the increase of plasma LDL level.

There were some reports that dysregulated adipose tissue, as seen in cases of obesity and lipoatrophy, raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes and cardiovascular disease.[5,6] Recent research on cross-talk of adipose tissue with other organs by the adipocytokines and other proteins, one of which is known for ApoE.[7] Other articles on ApoE function of body fatness regulation were reported.[8-10] Of those study, one large study known as The Atherosclerosis Risk in Communities (ARIC) Study has reported that the ApoE isoforms are associated with increasing body mass index in the order: ApoE2> ApoE3>ApoE4.[9] Other epidemiologic study have represented that the presence of at least one ApoE4 allele is associated with a greater risk of coronary artery disease.[11,12] Which increasing risk could be from elevated plasma LDL cholesterol, a well-established risk factor in the field of lipid-lowering treatment.[13,14]

There is no previous report on the ApoE polymorphism related to the LDL cholesterol and other metabolic parameters in the postmenopausal Korean women. Therefore, we investigated how serum LDL level is related to various isoforms of ApoE polymorphism in association with obesity and metabolic syndrome.

MATERIALS AND METHODS

Study subjects and design

Three hundreds thirty two postmenopausal Korean women were enrolled, whose data came from their routine health check-up after informed consent for this study to evaluate the ApoE polymorphism and metabolic abnormalities in the Health Promotion Center, Ajou University Hospital, Suwon, South Korea, from 2002 to 2004. The socioeconomic status of the subjects was relatively high, because most of the subjects were housewives of the executives in one big, well-known company in Korea. They all gave the informed consent, and Institutional Review Board of Ajou University Hospital approved this study.

Study design

Using the data of study subjects which were gathered for three years, ApoE polymorphism, including LDL cholesterol, and anthropometry, we compared the presence of obesity, metabolic syndrome, and related metabolic parameters according to their ApoE polymorphism. To be consistent with previous publications,[15] we defined three ApoE isoform groups: 1) the ApoE2 group included those subjects carrying the E2/E2 or E3/E2 or E4/E2 genotype; 2) the ApoE3 group included those carrying the E3/E3 genotype; and 3) the ApoE4 group included those carrying the E4/E3 or E4/E4 genotype. Additionally, we evaluated the odds ratios of having highest LDL-cholesterol among ApoE isoforms with or without obesity.

Measurements

Anthropometry and laboratory test

Height and body weight of the participants were measured while they were light clothing without shoes. Weight was measured to the nearest 0.1 kg, and height was measured to the nearest centimeter. Body mass index was calculated as the weight divided by height squared (BMI, kg/m^2). Trained nurses measured the waist circumference between the lower rib and the iliac crest, and electrically measured blood pressure after the participants had been at rest for at least 15 minutes (TM-2655P; PMS Instruments, Higashi-Ikebukuro, Toshima-Ku, Tokyo, Japan). Additionally, all of the subjects underwent blood test [standard enzymatic measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and fasting glucose in fresh serum samples (TBA-200FR, Toshiba, Tokyo, Japan)].

Genetic analysis of ApoE

Leukocyte DNA was derived from 5-10 mL of whole blood as previously described.[16] ApoE genotyping was performed as described by Hixson and Vernier.[17] A 244 bp sequence of the ApoE gene, including the two polymorphic sites, was amplified by PCR in a DNA Thermal Cycler (PTC-100; MJ Research, Watertown, MA, USA), using oligonucleotide primers F4 and F6. Each reaction mixture was heated at 94°C for 2 minutes, followed by 35 cycles of amplification (94°C for 40 s, 62°C for 30 s, and 72°C for 1 min). The PCR products were digested with 5 units of *Hha*I, and the fragments were separated by electrophoresis on an 8% polyacrylamide nondenaturing gel. After electrophoresis, the gel was treated with ethidium bromide for 30 min, and DNA fragments were visualized by ultraviolet illumination.

The definition of obesity and metabolic syndrome in this study

Obesity was defined as BMI≥25 kg/m^2, using body weight and height in all subjects, according to the Asian guideline, and central obesity was also defined as waist circumference ≥90 cm for men and ≥85 cm for women, defined in 2006 by Korean Society of Study of Obesity.[18] We followed NCEP-ATP III Asian guideline[19] components to define metabolic syndrome, which are consisted of central obesity (waist circumference≥90 cm for men and ≥85 cm for women), blood pressure≥130/80 mmHg, triglyceride≥150 mg/dL, fasting glucose≥110 mg/dL, and low high-density lipoprotein cholesterol (men<40 mg/dL, women<50 mg/dL). In that guideline, subjects who have more than 3 abnormal values mentioned above were defined as metabolic syndrome subjects.

Statistics

Chi-square tests to compare proportions across all ApoE isoforms (E2, E3, E4) and metabolic syndrome, obesity groups, and ANOVA test to compare means of continuous variables such as various metabolic parameters across all groups were used. Analysis of covariance was used to determine the LDL level among ApoE groups, adjusting for covariates such as age, BMI, blood pressure, HDL, logTG, fasting blood sugar, daily activity and regular exercise. Multivariate logistic analysis was done to evaluate the odds ratio of having highest quartile of LDL cholesterol.

RESULTS

Table 1 shows baseline characteristics of all study subjects. Their mean age was 61.8 years, and they were all postmenopausal Korean women. Mean BMI was 23.7, indicating that overall body weight of subjects was overweight. Mean values of metabolic parameters, including waist circumference, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, and fasting blood sugar, showed normal ranges. ApoE is composed of six genotypes, E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4, therefore, we simply grouped them into three groups by following previous publications; E2 (E2/2, E2/3, E2/4), E3 (E3/3), E4 (E3/4, E4/4). Proportions of each genotypes were 20.8% (n=69), 60.2% (n=200), and 19% (n=63), respectively. ApoE3/3 isoform had higher prevalence of metabolic syndrome and obesity than other ApoE isoforms (Fig. 1). In addition, the comparisons between ApoE isoforms and metabolic pa-

Table 1. Baseline Characteristics of Study Subjects

Variables		Women (n=332)
Age (yrs)		61.8±5.9
Height (cm)		155.9±5.2
Body weight (kg)		57.8±7.1
BMI (kg/m^2)		23.7±2.7
Wc (cm)		76.5±6.4
s-BP (mmHg)		128.2±16.5
d-BP (mmHg)		78.3±10.3
TC (mg/dL)		198.4±35.3
HDLC (mg/dL)		54.3±15.2
LDLC (mg/dL)		104.3±48.4
TG (mg/dL)		126.6±77.9
FBS (mg/dL)		108.4±110.2
E2 (n=69)	E2/E2 (%)	1 (0.3)
	E2/E3 (%)	54 (16.3)
	E2/E4 (%)	14 (4.2)
E3 (n=200)	E3/E3 (%)	200 (60.2)
E4 (n=63)	E3/E4 (%)	55 (16.6)
	E4/E4 (%)	8 (2.4)
Hypertension		23 (6.9%)
Diabetes		20 (6%)

All values are mean±stadard deviation. BMI is calculated from body weight (kg)/height (m^2). E2; including E2/E2, E2/E3, E2/E4. E3; including E3/E3. E4; including E3/E4, E4/E4.

Wc, waist circumference; s-BP, systolic blood pressure; d-BP, diastolic blood pressure; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG, triglyceride; FBS, fasting blood sugar.

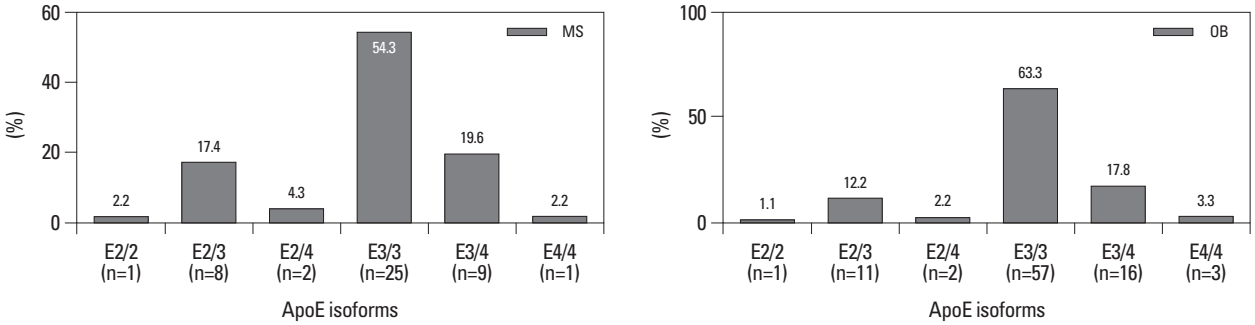

Fig. 1. The prevalence of metabolic syndrome and obesity according to the ApoE isoforms. This figure represents the prevalence of metabolic syndrome and obesity according to the ApoE isoforms. ApoE3/3 isoform showed higher prevalence of metabolic syndrome and obesity than other ApoE isoforms (p<0.05). MS, metabolic syndrome; OB, obesity.

rameters showed that the difference in total cholesterol and LDL cholesterol, between the groups was also significant after adjustment of age, BMI, blood pressure, HDL, LogTG, fasting blood sugar, and daily physical activity (Table 2). ApoE3 isoform showed significantly higher LDL cholesterol and total cholesterol than ApoE2 isoform (Fig. 2). ApeE4 isoform was not significantly different in the level of LDL-C compared to the other types of ApoE.

We divided LDL cholesterol by quartiles and compared the odds ratios of having the highest LDL cholesterol quartile among ApoE isoforms with or without obesity and metabolic syndrome. We set ApoE2 isoform without obesity or metabolic syndrome as reference group. ApoE3 isoform with obesity (OR=3.46, 95% CI; 1.07-11.14, p=0.037) or metabolic syndrome (OR=5.06, 95% CI; 1.14-22.29, p=0.037) showed significantly higher odds ratio of having the highest quartile of LDL cholesterol, compared to ApoE2 isoform without obesity or metabolic syndrome, after age adjustment. Additionally, the odds ratio of ApoE4 isoform was not significant compared to the ApoE3 isoform, even though the odds ratios were higher than those of the ApoE3 isoform (Table 3).

DISCUSSION

In our cross-sectional study, we found that postmenopausal Korean women had various ApoE isoforms, however, over half of subjects had ApoE3 (E3/3, 60.2%) isoform, which was similar to previous studies. In metabolic concern, ApoE3 isoform showed higher LDL cholesterol than ApoE2 (E2/2, E2/E3, E2/E4) isoform. In addition, the odds ratio of having the highest LDL cholesterol quartile in each ApoE isoform with or without obesity or metabolic syndrome was 3.46 in ApoE3 isoform with obesity, and 5.06 with metabolic syndrome compared to ApoE2 without obesity or metabolic syndrome, respectively, showing significant difference.

Previous studies showed that increased risk of CHD associated with having small, dense LDL particles might be modulated to a significant extent by the presence/absence of insulin resistance, abdominal obesity and increased LDL particle concentration,[20] and that the risk attributable to small LDL particles might partly be independent of the concomitant variation in plasma lipoprotein-lipid concen-

Table 2. Comparisons of Metabolic Parameters According to the ApoE Isoforms

Variables	E2 (n=69)	E3 (n=200)	E4 (n=63)	p value
Ages (yrs)	62.2 (5.6)	61.9 (6.0)	61.0 (6.1)	0.442
Wc (cm)	74.4 (4.3)	75.6 (3.5)	75.2 (3.5)	0.775
s-BP (mmHg)	129.0 (17.3)	127.8 (16.9)	128.4 (14.3)	0.885
d-BP (mmHg)	78.7 (10.6)	78.1 (10.7)	78.7 (9.1)	0.890
TC (mg/dL)	184.8 (33.6)	202.5 (34.0)	199.6 (38.2)	0.002*
HDL (mg/dL)	55.8 (15.4)	54.3 (15.1)	52.4 (15.7)	0.470
LDL (mg/dL)	85.6 (47.2)	109.7 (46.0)	106.8 (53.0)	0.002*
Log TG (mg/dL)	2.02 (0.23)	2.05 (0.21)	2.08 (0.24)	0.396
FBS (mg/dL)	99.5 (16.7)	112.6 (139.9)	104.7 (29.6)	0.690

All values are mean (standard deviation). E2; including E2/E2, E2/E3, E2/E4. E3; including E3/E3. E4; including E3/E4, E4/E4.
Wc, waist circumference; s-BP, systolic blood pressure; d-BP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Log TG, log-transformed TG.
All p values are from ANOVA test before adjustment.
*p<0.05 using ANCOVA test after adjustment including age, BMI, s-BP, d-BP, HDL, Log TG, FBS, and daily physical activity.

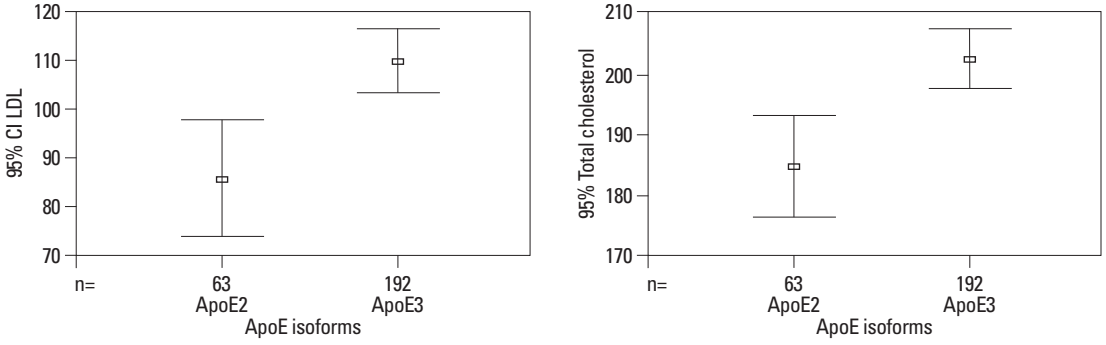

Fig. 2. The relationship between ApoE isoforms, LDL-cholesterol, and Total cholesterol level. This figure represents LDL-cholesterol (above) and Total cholesterol level according to the ApoE isoforms. E2 type has low LDL-cholesterol and total cholesterol level compared to the E3 type. E2; including E2/E2, E2/E3, E2/E4, E3; including E3/E3.

Table 3. Odds Ratios of Having Highest Quartile of LDL-Cholesterol in Each ApoE Isoform and the Presence of Obesity or Metabolic Syndrome

Isoforms	OB (-) (95% CI)	OB (+) (95% CI)	MS(-) (95% CI)	MS(+) (95% CI)
E2	1 (n=48)	n.s (n=14)	1 (n=46)	n.s (n=11)
E3	1.54 (0.51-4.64, n=130)	3.46 (1.07-11.14, n=57)	2.69 (0.79-9.11, n=143)	5.06 (1.14-22.39, n=25)
E4	3.00 (0.79-11.30, n=41)	2.40 (0.51-11.18, n=19)	3.90 (0.98-15.47, n=44)	9.01 (0.71-113.88, n=10)

Logistic regression analysis was done using by logistic regression analysis after age-adjustment.
Mean level (standard deviation) of the highest quartile of LDL cholesterol was 158.6 (19.1). ApoE3 with obesity group showed significant elevated odds ratio (OR=3.46, P=0.037) compared to the ApoE2 without obesity (Reference group), ApoE3 with metabolic syndrome group also showed significant elevated odds ratio (OR=5.06, P=0.032) compared to the ApoE2 without metabolic syndrome (Reference group).
n.s; odds ratio of ApoE2 with obesity and ApoE2 with metabolic syndrome showed not significant data due to small subject numbers.

trations.[21] Furthermore, insulin sensitivity is also important, because it is a significant predictor of LDL size, and together with age and BMI, it is also independent contributor to the variance of LDL size.[22] In addition, dyslipidemia associated with insulin resistance and obesity includes effects on lipoprotein metabolism that are missed when traditional lipoprotein cholesterol and total TG are examined. Lipoprotein size and subclasses should also be examined in studies investigating the roles of insulin resistance and obesity in the pathogenesis and prevention of atherosclerosis.[23]

It has been known that ApoE is a key player in adiposity, insulin sensitivity and glucose homeostasis, which deficient mice have less body fat, and the adipocytes in their white adipose tissues are smaller than those in wild-type mice when both are fed a high-fat diet.[24,25] Other studies showed that the two isoforms, ApoE3 and ApoE4, have significantly different influence on lipid-related diseases.[26,27] As for the affinity of LDL receptors, ApoE4 has a somewhat higher affinity for the LDL receptor than ApoE3[28] and cholesterol efflux from cells expressing ApoE4, such as macrophages and neurons, is less efficient than cells expressing other isoforms.[29,30] In comparison with other ApoE isoforms, it is known that ApoE2 binds poorly to the LDL receptor and is associated with type III hyperlipidemia.[4] In our study, however, subjects who had ApoE3 isoform showed higher LDL level than ApoE2 isoforms, and BMI of ApoE3 showed significant increase compared to the previous report.[9] In addition, most of our study subject were not obese, however, subjects who have ApoE3 isoform can have higher LDL level compared to ApoE2, which can affect the risk of cardiovascular disease. Therefore, our results may indicate that postmenopausal Korean women who have ApoE2 isoform can have lower risk of IHD by oxidized LDL due to lower LDL cholesterol level, and that women who have ApoE3 isoform can have higher risk of IHD compared to women who have ApoE2 isoform. However, further prospective research is needed to evaluate the relationship between the cardiovascular event or mortality and ApoE polymorphism, especially ApoE2, E3, E4. In case of ApoE4, the odds ratio of having the highest quartile of LDL-cholesterol was higher than those of ApoE3, but there was no significance in statistical aspect. That result might have been due to relatively small frequency of ApoE4 compared to the ApoE3[31] or there in no component on LDL-cholesterol in defining the metabolic syndrome. Further study is needed to find out that result.

There are several limitations in this study. We analyzed the data of postmenopausal Korean women, which may have critical selection bias to interpret the various LDL cholesterol level and obesity. And not all subjects were not obese (29.1%) and there were no results on men. Most of subjects were high economic status group. In addition, we didn't carry out full adjustment to evaluate the difference of each ApoE isoforms such as smoking (most of subjects were non-smokers), alcohol consumption, exercise time, sleep time and so on.

In conclusion, ApoE3 isoform among ApoE polymorphism was significantly correlated with higher serum LDL than other ApoE isofoms. Serum LDL cholesterol was positively associated with obesity or metabolic syndrome in ApoE3 isoform. This study suggests that obesity or metabolic syndrome risk should effectively be managed in postmenopausal Korean women with ApoE3 isomform to reduce serum LDL.

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