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ARTICLE

Longitudinal interaction between *APOA5* -1131T>C and overweight in the acceleration of age-related increase in arterial stiffness through the regulation of circulating triglycerides

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Abstract

We aimed to evaluate whether the longitudinal interaction between *APOA5*-1131C variants and overweight could accelerate age-related increases in arterial stiffness and circulating triglycerides in healthy subjects. This 3-year prospective cohort study included 503 healthy subjects. Brachial-ankle pulse wave velocity (baPWV), triglycerides, *APOA5* -1131T > C, apolipoprotein (apo) A-V level, and low-density lipoprotein (LDL) particle size were measured at baseline and within a mean follow-up period of 3 years. At the 3-year follow-up, in the overweight group, subjects with the C allele showed increases in triglycerides and baPWV relative to baseline. Additionally, in the overweight group, there was a genotype effect on changes in triglycerides: subjects with the C allele had greater increases in triglyceride concentrations than subjects with the TT genotype. Furthermore, overweight subjects with the C allele had greater increases in triglyceride concentrations than normal-weight subjects with the C allele (*P*-interaction = 0.013). Overweight subjects with the C allele had greater increases in baPWV than normal-weight subjects with the C allele (*P*-interaction = 0.047). Changes in baPWV were affected by age, baseline baPWV, and changes in systolic blood pressure (BP) and triglycerides. Changes in triglycerides were affected by *APOA5* -1131T > C genotype, age, baseline triglyceride level, and changes in BMI and apo A-V. In the overweight group, changes in baPWV were affected by changes in systolic BP, LDL particle size, and triglycerides. This prospective study shows that the interactive effect between *APOA5* -1131C variants and overweight can accelerate age-related increase in arterial stiffness via the regulation of circulating triglycerides in healthy subjects.

Keywords *APOA5* · Arterial stiffness · Gene-environment interaction · Overweight · Triglycerides

Introduction

The *APOA5* gene, encoding apolipoprotein (apo) A-V, is one of the major genetic determinants of circulating triglyceride levels, as demonstrated in animal models [1]. In humans, both single-gene and genome-wide association studies in different populations have confirmed the importance of *APOA5* in affecting triglyceride concentrations [2, 3]. Circulating triglyceride levels, which are also affected by overweight/obesity and insulin resistance [4], are a risk factor for atherosclerosis [5] and can initiate atherogenic dyslipidemia [6].

In clinical practice, pulse wave velocity (PWV) is widely used to reflect arterial stiffness, an index of atherosclerosis [7, 8]. Brachial-ankle PWV (baPWV) measurements, which are easier to perform than carotid-femoral PWV measurements, have been used as a marker to screen for vascular damage and cardiovascular risk in the general population [7, 9]. Deterioration of arterial stiffness has been associated with hospitalization for various forms of new-onset cardiovascular disease, such as heart failure [10]. A cardiovascular outcome resulting from hypertriglyceridemia is

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arterial stiffness, a pathological condition associated with vascular damage [7]. An inverse relationship between plasma triglycerides and plasma apo A-V and between hepatic *APOA5* expression and plasma triglyceride levels has been described in an animal-model study [1], whereas an unexpected and significant positive correlation between circulating apo A-V and triglyceride levels in men and women has been demonstrated [11, 12]. This difference might be because most human studies examining the relationship between apo A-V and triglycerides are cross-sectional.

Recent literature has shown that increasing muscle strength is a positive factor that leads to reductions in arterial stiffness in overweight/obese females [13]. Although improvements in muscle strength may affect arterial stiffness, which increases with age, longitudinal interactions between genetic and environmental factors that might influence the progression of arterial stiffness remain unknown. Thus, studies exploring the longitudinal effect of *APOA5* -1131T > C on the age-related progression of arterial stiffness and circulating concentrations of triglycerides and apo A-V are necessary. In this study, we examined whether the longitudinal interaction between *APOA5* -1131T > C (TT vs. C allele) and body weight (normal-weight vs. overweight) affects the age-related progression of arterial stiffness and the circulating levels of triglycerides and apo A-V of healthy subjects.

Methods

Subjects

We performed a 3-year prospective cohort study that included 800 heathy subjects (30–65 years old), who underwent triennial medical evaluations at the National Health Insurance Corporation Ilsan Hospital in Goyang, Korea during the period from January 2008 to December 2013. Of these, 503 nondiabetic and nonobese individuals were finally selected. Exclusion criteria included the following: (1) current and/or past history of cardiovascular disease, (2) diabetes mellitus (fasting glucose levels ≥ 126 mg/dL), (3) abnormal liver or renal function, (4) thyroid or pituitary disease, (5) pregnancy or lactation, and (6) regular use of any medication. Before participation, the purpose of the study was carefully explained to all participants, and their written informed consent was obtained. The study protocol was approved by the Institutional Review Board of the National Health Insurance Corporation Ilsan Hospital and Yonsei University and was carried out in accordance with the Helsinki Declaration. Sample size was determined and calculated using the 'pwr' package in R software v.3.4.1 (https://cran.r-project.org/). In an exploratory pilot study, the triglyceride level in the normal-weight group was 87.9 ± 48.4 mg/dL (mean ± standard deviation), which was lower than the triglyceride level in the overweight group (129.4 ± 68.7 mg/dL). The sample size was determined via a two-sample *t*-test calculation with an effect size of $d = 0.698$, a power of 0.8, and a level of significance of $\alpha = 0.05$. The results indicated that a minimum of 33 subjects per group were necessary; therefore, we selected more subjects than this minimum to increase the statistical power of our analysis.

Genotyping of rs662799 (*APOA5* -1131T > C)

Among the five common *APOA5* SNPs that have been studied, -1131T > C and 56 C > G (S19W) are considered to be functional tag SNPs [1, 14, 15]. However, the S19W SNP was monomorphic in the population of this study. Thus, the *APOA5* -1131T > C SNP was selected as the functional SNP to investigate further. Genotyping was performed via SNP-IT™ assays using single primer extension technology (SNPstream 25 K™ System, Orchid BioSciences, NJ). Detailed methods for the genotyping have been previously described [16].

Clinical and biochemical assessments

Detailed information on the clinical and biochemical assessments have been described in a previous paper [17]. Body weight, height and waist circumference were measured, and body mass index (BMI) was calculated in units of kilograms per square meter (kg/m^2). Systolic and diastolic blood pressure (BP) was assessed in a supine position after a resting period. Blood samples were collected following an overnight fast of at least 12 h. Fasting triglycerides, total, and high-density lipoprotein (HDL) cholesterol, glucose, insulin, low-density lipoprotein (LDL) particle size, and apo A-V were measured as previously described [17]. baPWV was measured using an automatic waveform analyzer (model VP-1000; Nippon Colin Ltd., Komaki, Japan).

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM/SPSS, Chicago, IL, USA). Hardy-Weinberg equilibrium (HWE) was tested for using PLINK version 1.07 (http://pngu.mgh.harvard.edu/purcell/plink/). Differences in clinical variables between two groups (normal-weight vs. overweight or TT vs. C allele) were tested using independent *t*-tests. Paired *t*-tests were performed to determine the differences at the 3-year follow-up from the baseline in each group. The interactions between genotype and bodyweight were tested using a two-way ANOVA. Multiple linear regression analyses were performed to

identify major independent predictors of changes in baPWV and triglyceride levels. *Pearson*'s correlation coefficient was used to examine the relationships between variables. Heat maps were created to visualize and evaluate the relationships among metabolites and the biochemical measurements in the study population. Logarithmic transformations were performed on skewed variables. For descriptive purposes, the mean values are presented as untransformed values. The results are expressed as the means ± standard error (SE). A two-tailed P-value < 0.05 was considered statistically significant.

Results

Distribution of rs662799 (*APOA5* -1131T > C) in normal-weight and overweight subjects

We divided the cohort into 2 groups: the normal-weight group ($18.5\ kg/m^2 \le BMI < 25\ kg/m^2$, $n = 349$) and the overweight group ($25\ kg/m^2 \le BMI < 30\ kg/m^2$, $n = 154$). The genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium ($P > 0.05$). The frequencies of the minor alleles of *APOA5* -1131T > C were 0.297 and 0.315 in normal-weight and overweight individuals, respectively, which are similar to the values observed in the Korean population [18]. Among the 349 normal-weight individuals, 168 were homozygous (TT) for the T allele, 155 were heterozygous for the C allele (TC) and 26 were homozygous (CC) for the C allele of the *APOA5* -1131T > C polymorphism. Among the 154 overweight individuals, 68 were homozygous (TT) for the T allele, 75 were heterozygous for the C allele (TC) and 11 were homozygous (CC) for the C allele of the *APOA5* -1131T > C polymorphism. We pooled the heterozygotes (TC) and rare-allele homozygotes (CC) to increase statistical power.

Clinical characteristics and biochemical parameters at baseline and the 3-year follow-up

With regard to the *APOA5* -1131T > C polymorphism, there were no significant differences between the normal-weight and overweight groups at baseline in their age and sex distributions across the genotypes (Table 1). Additionally, there were no significant differences in smoking or drinking status across the genotypes in the normal-weight and overweight groups at baseline and at the 3-year follow-up (data not shown). In the normal-weight group, there was no *APOA5* -1131T > C genotype effect at baseline, but at the 3-year follow-up, a genotype-effect was found in relation to HDL cholesterol: HDL cholesterol levels were lower in normal-weight individuals with the C allele than in those with the TT genotype (Table 1).

The overweight group showed higher BMI values, systolic and diastolic BP, and glucose and insulin levels and lower HDL cholesterol levels at both baseline and the 3-year follow-up than the normal-weight group, irrespective of genotype. Overweight individuals with the C allele showed higher total cholesterol levels at baseline and a smaller LDL particle size at both baseline and the 3-year follow-up. After 3 years, overweight C allele carriers showed significant increases in systolic BP and a significant decrease in HDL cholesterol relative to baseline. At the 3-year follow-up in the overweight group, C allele carriers showed lower HDL cholesterol levels and a smaller LDL particle size than TT carriers (Table 1).

Interaction between the *APOA5* -1131T > C genotype and body weight in relation to 3-year changes in triglycerides, apo A-V, systolic BP and baPWV

The effects of the *APOA5* -1131T > C genotype on mean changes in triglycerides, apo A-V, and baPWV in the normal-weight and overweight groups at 3 years are shown in Fig. 1. In the normal-weight group, individuals with the C allele showed higher serum triglyceride levels than those with the TT genotype. The overweight group showed higher serum triglyceride levels at both baseline and the 3-year follow-up than the normal-weight group, irrespective of genotype. After 3-years, overweight C allele carriers showed significant increases in triglycerides and baPWV. At the 3-year follow-up, C allele carriers showed higher triglycerides than TT carriers in the overweight group. Furthermore, at the 3-year follow-up, overweight TT and C allele carriers showed higher baPWVs than normal-weight subjects with the TT and C alleles, respectively (Fig. 1).

The interaction of gene and body weight did not significantly affect changes in fasting apo A-V (Fig. 1), BP, HDL cholesterol, total cholesterol, glucose, insulin, or LDL particle size (data not shown). At the 3-year follow-up, after adjusting for age, sex, smoking and drinking, the results show a significant interaction between the *APOA5* -1131T > C genotype and body weight (overweight compared with normal-weight) in relation to changes in triglycerides (P for interaction = 0.013) and baPWV (P for interaction = 0.047). In the overweight group, there was an *APOA5* -1131T > C genotype effect on changes in triglycerides: subjects with the C allele had greater increases in serum triglyceride concentrations than subjects with the TT genotype. However, this genotypic effect on changes in triglycerides was not observed in normal-weight subjects. Additionally, overweight subjects with the C allele had greater increases in serum triglyceride concentration than normal-weight subjects with the C allele. Overweight subjects with the C allele also had greater increases in baPWV

Table 1 Biochemical parameters according to rs662799 (*APOA5* -1131 T > C) genotype at baseline and 3-year follow-up in healthy individuals who were normal-weight or overweight

	Normal-weight				Overweight			
	TT ($n = 168$)		C allele ($n = 181$)		TT ($n = 68$)		C allele ($n = 86$)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Baseline age (year)	47.7 ± 0.67		47.3 ± 0.70		47.6 ± 1.14		47.4 ± 1.05	
Male/Female *n*, (%)	76 (45.2)/92 (54.8)		79 (43.6)/102 (56.4)		28 (41.2)/40 (58.8)		41 (47.7)/45 (52.3)	
BMI (kg/m^2)	22.1 ± 0.14	22.2 ± 0.16	22.0 ± 0.14	22.1 ± 0.15	26.8 ± 0.18[a]	27.0 ± 0.22[b]	26.8 ± 0.19[c]	26.7 ± 0.23[d]
Change	0.10 ± 0.08		0.10 ± 0.07		0.08 ± 0.15		−0.08 ± 0.11	
Systolic BP (mmHg)	115.5 ± 1.08	116.7 ± 1.03	115.2 ± 0.90	115.1 ± 1.01	121.6 ± 1.65[a]	123.4 ± 1.73[b]	122.7 ± 1.38[c]	126.1 ± 1.35[d,*]
Change	1.15 ± 0.92		−0.10 ± 0.89		1.76 ± 1.71		3.35 ± 1.34[e]	
Diastolic BP (mmHg)	70.9 ± 0.83	71.8 ± 0.81	70.7 ± 0.74	71.5 ± 0.76	75.2 ± 1.22[a]	76.8 ± 1.26[b]	75.4 ± 1.01[c]	77.4 ± 1.04[d]
HDL cholesterol (mg/dL)[f]	56.3 ± 1.08	55.3 ± 0.93	53.9 ± 1.11	52.0 ± 1.05[g,*]	52.4 ± 1.68[a]	49.0 ± 1.53[b,*]	47.2 ± 1.27[h,c]	44.6 ± 1.16[i,d,*]
Total cholesterol (mg/dL)[f]	187.1 ± 2.34	195.0 ± 2.45[***]	184.8 ± 2.43	194.0 ± 3.07[***]	193.2 ± 3.80	195.6 ± 4.43	197.7 ± 3.42[c]	200.7 ± 3.38
Glucose (mg/dL)[f]	91.2 ± 0.65	92.0 ± 0.59	90.0 ± 0.64	90.5 ± 0.75	95.2 ± 1.18[a]	97.4 ± 1.53[b]	97.0 ± 0.93[c]	96.7 ± 1.22[d]
Insulin (μIU/dL)[f]	8.12 ± 0.27	7.31 ± 0.20[*]	7.93 ± 0.22	7.13 ± 0.23[***]	10.2 ± 0.46[a]	9.72 ± 0.51[b]	9.77 ± 0.42[c]	9.02 ± 0.44[d,*]
LDL particle size (nm)[f]	23.8 ± 0.07	23.9 ± 0.10	23.8 ± 0.07	23.8 ± 0.08	23.5 ± 0.18	23.6 ± 0.16	23.3 ± 0.14[c]	23.2 ± 0.17[i,d]

Note: Mean ± SE

[a] $P < 0.05$ for the comparison between subjects with the TT genotype in the normal-weight and overweight groups at baseline

[b] $P < 0.05$ for the comparison between subjects with the TT genotype in the normal-weight and overweight groups at 3-year follow-up

[c] $P < 0.05$ for the comparison between subjects with the C allele in the normal-weight and overweight groups at baseline

[d] $P < 0.05$ for the comparison between subjects with the C allele in the normal-weight and overweight groups at 3-year follow-up

[e] $P < 0.05$ for the comparison of changes in values between subjects with the C allele in the normal-weight and overweight groups

[f] tested by logarithmic transformation

[g] $P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the normal-weight group at 3-year follow-up

[h] $P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the overweight group at baseline

[i] $P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the overweight group at 3-year follow-up

[*] $P < 0.05$, [**] $P < 0.01$, and [***] $P < 0.001$ compared with the baseline levels in the appropriate group by paired *t*-tests

than normal-weight subjects with the C allele. Similarly, overweight subjects with the C allele had greater increases in systolic BP than normal-weight subjects with the C allele (Table 1); however, there was no significant effect of a gene × body weight interaction on systolic BP.

Correlation among changes in BMI, systolic and diastolic BP, triglycerides, HDL and total cholesterol, glucose, insulin, LDL particle size, apo A-V, and baPWV

Figure 2 shows correlations among changes (differences from baseline) in BMI, systolic and diastolic BP, triglycerides, HDL cholesterol, total cholesterol, glucose, insulin, LDL particle size, apo A-V, and baPWV values in the normal-weight and overweight groups according to *APOA5* -1131T > C genotype. In the normal-weight group with the TT genotype, changes in triglycerides correlated positively with changes in BMI, glucose, and insulin values and negatively with changes in LDL particle size and apo A-V level ($P < 0.001$, Fig. 3). Changes in baPWV were positively correlated with changes in glucose level and systolic and diastolic BP in the normal-weight group with the TT genotype. In the normal-weight group with the C allele, changes in triglycerides correlated negatively with changes in HDL cholesterol level and LDL particle size and positively with changes in BMI, insulin level and baPWV ($P = 0.011$, Fig. 3), which was positively correlated with changes in systolic and diastolic BP in the normal-weight group with the C allele. In the overweight group with the TT genotype, changes in triglycerides were negatively correlated with changes in LDL particle size and apo A-V level ($P = 0.002$, Fig. 3). Changes in baPWV were positively correlated with changes in glucose level and systolic and diastolic BP in the normal-weight group with the C allele. In the overweight group with the C allele, changes in triglycerides correlated negatively with changes in HDL cholesterol and apo A-V levels ($P = 0.028$, Fig. 3) and LDL particle size and positively with changes in BMI, insulin level and baPWV ($P = 0.004$, Fig. 3), which was positively correlated with changes in systolic and diastolic BP in the overweight group with the C allele. Other correlations among the changes in clinical and biochemical parameters are shown in Fig. 2.

Because the regulation of changes in triglyceride levels is complex, a multiple linear regression analysis was performed that included all subjects ($n = 503$) to determine the

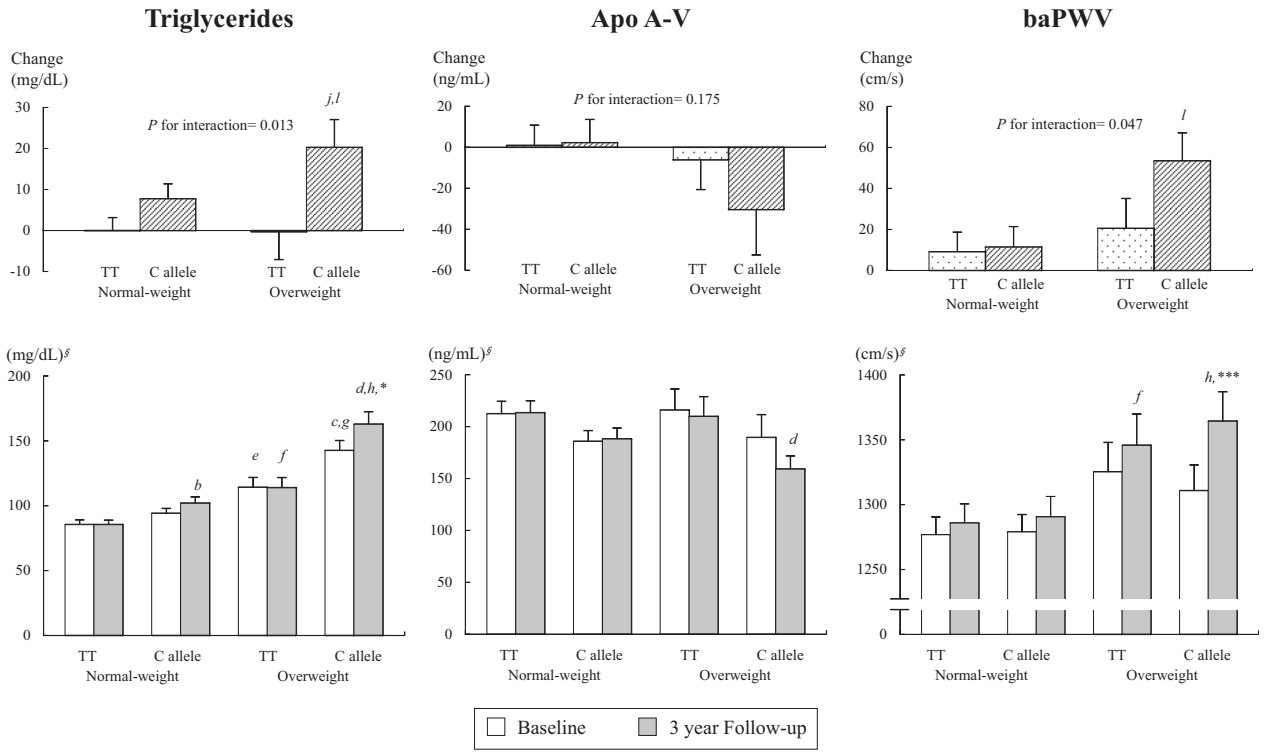

Fig. 1 Effect of the *APOA5* -1131T > C genotype on changes from baseline for triglycerides, LDL particle size, apo A-V, and baPWV in the normal-weight and overweight groups at 3-year follow-up. Mean ± SE. [§]tested by logarithmic transformation. [a]$P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the normal-weight group at baseline. [b]$P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the normal-weight group at 3-year follow-up. [c]$P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the overweight group at baseline. [d]$P < 0.05$ for the comparison between subjects with the TT genotype and subjects with the C allele in the overweight group at 3-year follow-up. [e]$P < 0.05$ for the comparison between subjects with the TT genotype in the normal-weight and overweight groups at baseline. [f]$P < 0.05$ for the comparison between subjects with the TT genotype in the normal-weight and overweight groups at 3-year follow-up. [g]$P < 0.05$ for the comparison between subjects with the C allele in the normal-weight and overweight groups at baseline. [h]$P < 0.05$ for the comparison between subjects with the C allele in the normal-weight and overweight groups at 3-year follow-up. [i]$P < 0.05$ for the comparison of changes in values between subjects with the TT genotype and subjects with the C allele in the normal-weight group. [j]$P < 0.05$ for the comparison of changes in values between subjects with the TT genotype and subjects with the C allele in the overweight group. [k]$P < 0.05$ for the comparison of changes in values between subjects with the TT genotype in the normal-weight and overweight groups. [l]$P < 0.05$ for the comparison of changes in values between subjects with the C allele in the normal-weight and overweight groups. [*]$P < 0.05$, [**]$P < 0.01$, and [***]$P < 0.001$ compared with levels at baseline for the appropriate group by paired *t*-tests

independent effects of the following variables on changes in triglycerides: age, *APOA5* -1131T > C genotype, and baseline triglyceride levels, as well as changes in BMI, systolic and diastolic BP and the levels of glucose, insulin, total and HDL cholesterol, and apo A-V. Changes in triglyceride in all subjects ($n = 503$) were affected by the *APOA5* -1131T > C genotype, age, baseline triglyceride level and by changes in BMI and apo A-V level ($R^2 = 0.258$, $P < 0.001$). In the normal-weight group ($n = 349$), changes in triglycerides were affected by baseline triglyceride levels and changes in BMI, glucose, apo A-V and systolic BP values ($R^2 = 0.286$, $P = 0.034$). In the overweight group ($n = 154$), changes in triglycerides were affected by baseline triglyceride levels and changes in apo A-V levels ($R^2 = 0.209$, $P = 0.013$).

We also performed a multiple linear regression analysis including all subjects ($n = 503$) to determine the independent effects of the following variables on changes in baPWV: age, *APOA5* -1131T > C genotype, baseline baPWV, as well as changes in BMI and systolic and diastolic BP and in the levels of glucose, insulin, total and HDL cholesterol, and apo A-V and LDL particle size. Changes in baPWV in all subjects ($n = 503$) were affected by age, baseline baPWV, and changes in systolic BP and triglyceride level ($R^2 = 0.193$, $P < 0.001$). In the normal-weight group ($n = 349$), changes in baPWV were affected by age, baseline baPWV and changes in triglyceride and apo A-V levels ($R^2 = 0.204$, $P = 0.032$). In the overweight group ($n = 154$), changes in baPWV were affected by changes in systolic BP, LDL particle size and triglyceride level ($R^2 = 0.413$, $P = 0.002$).

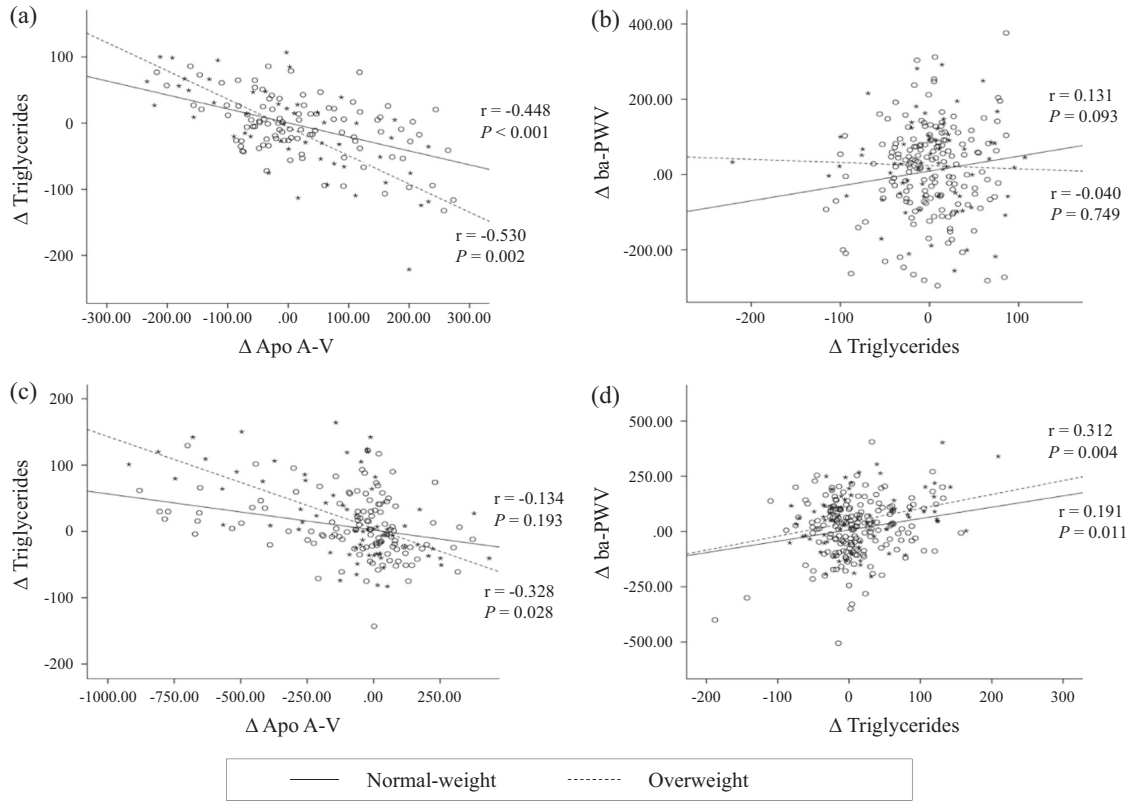

Fig. 2 Correlations between changes (Δ) in apo A-V and triglycerides and between changes in triglycerides and baPWV in the normal-weight (○) and overweight (*) groups according to *APOA5* -1131 T > C genotype. **a** Correlation between changes in apo A-V and triglycerides for subjects with the TT genotype. **b** Correlation between changes in triglycerides and baPWV for subjects with the TT genotype. **c** Correlation between changes in apo A-V and triglycerides for subjects with the TC or CC genotype. **d** Correlation between changes in triglycerides and baPWV for subjects with the TC or CC genotype

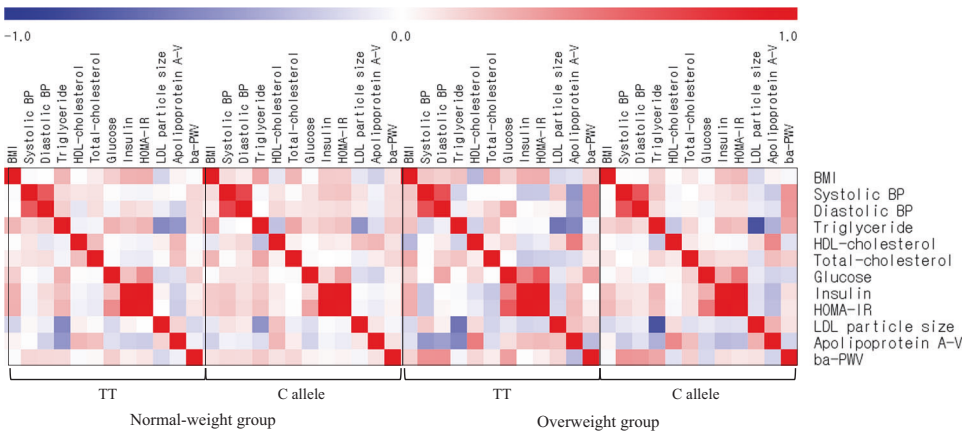

Fig. 3 Correlation matrix for changes in clinical parameters in the normal-weight and overweight groups according to *APOA5* -1131 T > C genotype. Correlations were obtained by deriving Pearson correlation coefficients. *Red* indicates a positive correlation, and *blue* indicates a negative correlation

Discussion

Arterial stiffness increases with age, but the interaction between genetic and environmental factors that might influence its progression are unknown. This prospective study examined the longitudinal interactive effects of *APOA5* -1131T > C and body weight on circulating triglycerides and the progression rate of arterial stiffness. baPWV, which reflects arterial stiffness [9, 19] was measured at baseline and re-examined within a mean follow-up period of 3 years. The main finding of this study is that the interactive effect between *APOA5* -1131C variants and overweight can accelerate the age-related elevation of arterial stiffness through the regulation of circulating triglyceride in healthy subjects.

At 3-years, the overweight group showed higher baPWVs than the normal-weight group, without considering genotype, but only the overweight subjects with the C allele showed an increase in baPWV over the 3-year period. Therefore, the overweight subjects with the C allele had greater increases in baPWV than the normal-weight subjects with the C allele. This result suggests that an acceleration in the age-related enhancement of arterial stiffness can partly result from a longitudinal interaction between *APOA5* -1131C variants and overweight. The existence of a strong association between the presence of metabolic syndrome, which includes elevated levels of circulating triglycerides, and arterial stiffness has been shown in many cross-sectional studies [9, 20, 21] and follow-up studies [7, 8, 22]. However, the longitudinal effect of triglyceride-related genes on arterial stiffness in the general population has not been clarified.

There was a significant and weakly positive correlation between the changes in triglycerides and in baPWV in the normal-weight group with the -1131C allele; however, a strongly positive correlation was present between the changes in triglycerides and baPWV in the overweight group with -1131C allele. This is partly due to the greater increases in triglycerides at the 3-year follow-up in the overweight C allele carriers than in those in the normal-weight group. These interactive effects between the *APOA5* gene and overweight on circulating triglyceride levels and arterial stiffness support the idea that circulating triglycerides play a role as one of the major inducers of arterial stiffness in overweight/obese subjects [4, 23, 24]. Recently, Guardiola et al. [2]. have shown that *APOA5* variants predispose hyperlipidemic patients to atherogenic dyslipidemia and subclinical atherosclerosis and that this predisposition is significantly stronger in subjects with BMI ≥ 25 kg/m^2 than in normal-weight subjects. In this study, a multiple linear regression analysis revealed that changes in triglycerides, systolic BP, and LDL particle size were independent determinants of the longitudinal progression of arterial stiffness in the subjects in the overweight groups.

The rare *APOA5* -1131C alleles were associated with an atherogenic profile characterized by high levels of small, dense LDL [2]. Atherogenic changes associated with LDL cholesterol induced by triglycerides have been found to occur at concentrations as low as 1.7 mmol/L, which is the level at which small, dense LDLs become predominant [25]. Recently, Vishnu et al [8]. found that baPWV was significantly associated with atherogenic small-sized LDL particles, independent of other cardiovascular risk factors. Takahashi et al [26]. also reported a significant association between very small LDL cholesterol and baPWV. Similarly, in the overweight group in this study, a change in LDL particle size was one of the independent determinants of a change in baPWV. At the 3-year follow-up, overweight subjects with the C allele showed smaller LDL particle sizes and lower plasma apo A-V concentrations than those with the TT genotype.

In all subjects, changes in triglycerides were independently affected by *APOA5* -1131T > C genotype, age, baseline triglyceride level, and changes in BMI and apo A-V levels. There were significant negative correlations between changes in triglycerides and plasma apo A-V concentrations in overweight individuals with the C allele and in TT carriers. This is in contrast to previous observations of significant positive correlations between circulating apo A-V and triglyceride levels in men and women [11, 12]. These different results could be partly explained by difference in study design. In general, previous human studies on the relationship between apo A-V and triglyceride levels have been cross-sectional; however, the current study was longitudinal. Moreover, significant negative correlations between changes in triglycerides and apo A-V were observed for subjects with the TT genotype regardless of body weight, whereas for C allele carriers, there was only a significant negative correlation in the overweight group. Subjects in the three groups with strong negative correlations between apo A-V and triglycerides, which included all subjects except for normal-weight individuals with the C allele, showed marked changes in triglycerides and apo A-V during the 3-year study period. However, normal-weight individuals with the C allele did not exhibit substantial changes in apo A-V during the study period despite having more dramatic changes in triglycerides. We can therefore speculate that insufficient changes in apo A-V may not affect correlations between changes in apo A-V and triglycerides. Future analysis would be necessary for further consideration of this interrelationship.

In terms of limitations, our study only included normal-weight and overweight subjects without diabetes or cardiovascular diseases; therefore, the present results may not extrapolate to subjects who are obese, diabetic or have cardiovascular diseases. In addition, we did not fully demonstrate regarding the exact underlying mechanisms of the genetic effects of *APOA5* -1131C allele in normal-weight group, thus, the further studies with a large sample size are needed. Despite this limitation, we found that the longitudinal interaction between *APOA5* -1131C variants and overweight could accelerate the age-related increase in arterial stiffness through the regulation of circulating triglycerides in healthy subjects. Therefore, the management of hypertriglyceridemia is important for preventing the progression to advanced arterial stiffness, especially in overweight subjects with the *APOA5* -1131C allele.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, et al. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001;294:169–73.
2. Guardiola M, Cofán M, de Castro-Oros I, Cenarro A, Plana N, Talmud PJ, et al. APOA5 variants predispose hyperlipidemic patients to atherogenic dyslipidemia and subclinical atherosclerosis. Atherosclerosis. 2015;240:98–104.
3. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. 2008;40:189–97.
4. Zaki M, Amr K. Apolipoprotein A5 T-1131C variant and risk for metabolic syndrome in obese adolescents. Gene. 2014;534: 44–47.
5. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010;375:1634–9.
6. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. Eur Heart J. 2013;34:1826–33.
7. Li CI, Kardia SL, Liu CS, Lin WY, Lin CH, Lee YD, et al. Metabolic syndrome is associated with change in subclinical arterial stiffness: a community-based Taichung community health study. BMC Public Health. 2011;11:808.
8. Vishnu A, Choo J, Masaki KH, Mackey RH, Barinas-Mitchell E, Shin C, et al. ERA JUMP Study Group. Particle numbers of lipoprotein subclasses and arterial stiffness among middle-aged men from the ERA JUMP study. J Hum Hypertens. 2014;28:111–7.
9. Hung CS, Lin JW, Hsu CN, Chen HM, Tsai RY, Chien YF, et al. Using brachial-ankle pulse wave velocity to associate arterial stiffness with cardiovascular risks. Nutr Metab Cardiovasc Dis. 2009;19:241–6.
10. Aisu H, Saito M, Inaba S, Morofuji T, Takahashi K, Sumimoto T, et al. Association of worsening arterial stiffness with incident heart failure in asymptomatic patients with cardiovascular risk factors. Hypertens Res. 2017;40:173–80.
11. Vaessen SF, Schaap FG, Kuivenhoven JA, Groen AK, Hutten BA, Boekholdt SM, et al. Apolipoprotein A-V, triglycerides and risk of coronary artery disease: the prospective Epic-Norfolk Population Study. J Lipid Res. 2006;47:2064–70.
12. Talmud PJ, Cooper JA, Hattori H, Miller IP, Miller GJ, Humphries SE. The apolipoprotein A-V genotype and plasma apolipoprotein A-V and triglyceride levels: prospective risk of type 2 diabetes. Results from the Northwick Park Heart Study II. Diabetologia. 2006;49:2337–40.
13. Alvarez-Alvarado S, Jaime SJ, Ormsbee MJ, Campbell JC, Post J, Pacilio J, et al. Benefits of whole-body vibration training on arterial function and muscle strength in young overweight/obese women. Hypertens Res. 2017;40:487–92.
14. Talmud PJ, Martin S, Taskinen MR, Frick MH, Nieminen MS, Kesäniemi YA, et al. APOA5 gene variants, lipoprotein particle distribution, and progression of coronary heart disease: results from the LOCAT study. J Lipid Res. 2004;45:750–6.
15. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. Hum Mol Genet. 2002;11:3031–8.
16. Kang R, Kim M, Chae JS, Lee SH, Lee JH. Consumption of whole grains and legumes modulates the genetic effect of the APOA5 -1131C variant on changes in triglyceride and apolipoprotein A-V concentrations in patients with impaired fasting glucose or newly diagnosed type 2 diabetes. Trials. 2014;15:100.
17. Kim M, Kim M, Lee YJ, Lee SP, Kim TS, Yang HJ, et al. Effects of α-linolenic acid supplementation in perilla oil on collagen-epinephrine closure time, activated partial thromboplastin time and Lp-PLA2 activity in non-diabetic and hypercholesterolaemic subjects. J Funct Foods. 2016;23:95–104.
18. Lim HH, Choi M, Kim JY, Lee JH, Kim OY. Increased risk of obesity related to total energy intake with the APOA5-1131T > C polymorphism in Korean premenopausal women. Nutr Res. 2014;34:827–36.
19. Tomiyama H, Hirayama Y, Hashimoto H, Yambe M, Yamada J, Koji Y, et al. The effects of changes in the metabolic syndrome detection status on arterial stiffening: a prospective study. Hypertens Res. 2006;29:673–8.
20. Ho CT, Lin CC, Hsu HS, Liu CS, Davidson LE, Li TC, et al. Arterial stiffness is strongly associated with insulin resistance in Chinese--a population-based study (Taichung Community Health Study, TCHS). J Atheroscler Thromb. 2011;18:122–30.
21. Wang F, Ye P, Luo L, Xiao W, Qi L, Bian S, et al. Association of serum lipids with arterial stiffness in a population-based study in Beijing. Eur J Clin Invest. 2011;41:929–36.
22. Safar ME, Thomas F, Blacher J, Nzietchueng R, Bureau JM, Pannier B, et al. Metabolic syndrome and age-related progression of aortic stiffness. J Am Coll Cardiol. 2006;47:72–75.
23. Satoh H, Saijo Y, Kishi R, Tsutsui H. Brachial-ankle pulse wave velocity is an independent predictor of incident hypertension in Japanese normotensive male subjects. Environ Health Prev Med. 2011;16:217–23.
24. Elosua R, Ordovas JM, Cupples LA, Lai CQ, Demissie S, Fox CS, et al. Variants at the APOA5 locus, association with carotid atherosclerosis, and modification by obesity: the Framingham Study. J Lipid Res. 2006;47:990–6.
25. Sniderman AD, Dagenais GR, Cantin B, Després JP, Lamarche B. High apolipoprotein B with low high-density lipoprotein cholesterol and normal plasma triglycerides and cholesterol. Am J Cardiol. 2001;87:792–3.
26. Takahashi R, Imamura A, Yoshikane M, Suzuki M, Murakami R, Cheng XW, et al. Very small low-density lipoprotein cholesterol level is a determinant of arterial stiffness in men with impaired glucose metabolism. J Atheroscler Thromb. 2010;17:1282–9.