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| 연구논문 |

Significant Association of ApoB/ApoA-I Ratio with Arterial Stiffness in Treated Hypertensive Patients

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Abstract: **Introduction:** Recent studies have demonstrated that the ratio of apolipoproteins B and apolipoprotein A-I is a better predictor of cardiovascular disease than conventional parameters of dyslipidemia. The purpose of this study was to determine whether apolipoprotein B/apolipoprotein A-I ratio is related to arterial stiffness in a population of treated, hypertensive patients.

Methods: The study group consisted of 657 treated hypertension patients. The pulse wave velocity was determined by measuring hfPWV and baPWV with a VP-1000 pulse wave unit.

Results: The average age of the study population was 55.9±10.1 years of age (range, 30 to 78) with 398 (60.7%) being male. The average ApoB level was 79.9±21.2 mg/dL and the average ApoAI level was 138.7±24.0 mg/dL. The average ApoB/ApoAI ratio was 0.60±0.19. The ApoB/ApoAI ratio was significantly lower in males due to the lower level of ApoAI. After controlling for age, gender, systolic blood pressure, heart rate, DM, body mass index (BMI), statins and smoking, ApoB/ApoAI was significantly associated with both hfPWV (R^2 = 0.505, β = 0.068, P = 0.020) and baPWV (R^2 = 0.480, β = 0.074, P = 0.013). Subgroup analysis revealed that the significant association of ApoB/ApoAI was significant only for the male population. [hfPWV (R^2 = 0.562, β = 0.108, P = 0.003) and baPWV (R^2 = 0.467, β = 0.104, P = 0.008)].

Conclusion: We demonstrated, for the first time, a significant association of ApoB/ApoAI with baPWV and hfPWV in treated, male hypertension patients, after adjustment for confounding factors and medications.

Keywords: *C-reactive protein, arteriosclerosis, hypertension*

1. Introduction

Previous epidemiological studies have demonstrated that increasing arterial stiffness is associated with development of systolic hypertension and increased risk of cardiovascular disease.[1-4] Recent studies have shown the prognostic importance of identifying arterial stiffness in treated hypertensive patients.[5,6] Therefore, identification of risk factors that are associated with arterial stiffness may be important in hypertensive patients. Although reduction of blood pressure can reduce arterial stiffness in hypertensive patients, there are other clinical factors involved in the development of arterial stiffness as well. [7]

Case control studies have demonstrated the significant association of conventional cardiovascular risk factors such as diabetes mellitus, hypertension and obesity on aortic stiffness.[8-11] Some studies have identified hypercholesterolemia as being significantly associatied with increasing arterial stiffness.[10,12] Recent studies have demonstrated that apolipoproteins B in atherogenic particles and anti atherogenic apolipoprotein A-I particles in HDLs are better predictors of cardiovascular disease than conventional parameters of dyslipidemia.[13-15] Because high proportion of patients with hypertension are associated with profiles of metabolic syndrome (MetS), that is normal to low LDL cholesterol with high triglyceride and low HDL cholesterol, the ratio of atherogenic particles and anti-atherogenic particles may have a greater predictive value. However, population studies regarding the association of apolipoprotein B/

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apolipoprotein A-I ratio with arterial stiffness in hypertensive patients have not been demonstrated.

Therefore, the purpose of this study was to determine whether apolipoprotein B/apolipoprotein A-I ratio is related to arterial stiffness, as determined by heart to femoral PWV (hfPWV) and brachial to ankle PWV (baPWV), in a population of treated, hypertensive patients.

2. Methods

Study population

Among a total of 859 treated hypertensive patients who underwent pulse wave velocity examination at Yonsei Cardiovascular Hospital between January 2004 and April 2005, we included 657 patients who underwent examination for Apolipoprotein B and Apolipoprotein A-I. For the purposes of this study, the study group consisted of subjects who were enrolled in the Yonsei Cardiovascular Genome center. The Cardiovascular Genome Center is a Korean government sponsored research project the objective of which is to determine the genetic factors that are associated with the development of cardiovascular disease in a large, prospective Korean cohort. Our database contained information about all the constituents of the MetS, and biochemical risk factors for CAD. Subjects were asked to refrain from performing strenuous exercise or drinking alcoholic beverages 24 hour before the laboratory test. They were also instructed to avoid eating or drinking anything except water during the test.

We recruited treating hypertensive subjects not only with diagnosis based on a systolic blood pressure of more than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg over three different visits prior to taking antihypertensive medication but also with taking medications currently for at least 3 months. Diabetes mellitus is defined as patients satisfying at least one of three criteria: 1) taking anti-diabetic medications, 2) fasting blood glucose level above 126 mg/dL and 3) random blood sugar above 200 mg/dL. Patients with any of the following conditions were excluded from participation: valvular heart disease, peripheral vascular disease, significant systemic disease, a history of inflammatory disease and on medication inflammatory, vasoactive drug, a clinically significant atrioventricular conduction disturbance, a history of atrial fibrillation or other serious arrhythmia, a history of congestive heart failure, severe hypertension (>210/130 mmHg) and serum creatinine greater than 1.4 mg/dL.

At the time of enrollment, patients underwent a complete physical examination, a baseline electrocardiogram, and a laboratory assessment. After resting at least five minutes in a sitting position, office blood pressure (BP) was measured using a sphygmomanometer with the appropriate cuff size. Two measurements were taken at least five minutes apart, and the mean BP was used for analysis. Blood chemistry (glucose, BUN, uric acid, total cholesterol, total bilirubin, alkaline phosphatase, AST, ALT, creatinine, Na, K, Triglyceride, HDL, LDL) and fasting serum insulin were assessed. The fasting serum insulin level was measured with an immunoradiometric assay and a gamma counter (Hewlett Packard, USA). The apolipoprotein B and apolipoprotein A assay was measured by immunoturbidimetry (Roche Diagnostics, Basel, Switzerland) as described previously.[16,17] This study was approved beforehand by the institutional ethics committee, and the procedures followed were in accordance with the institutional guidelines. All patients gave informed consent prior to being enrolled.

Pulse wave velocity measurement

The pulse wave velocity was determined by measuring hfPWV and baPWV with a VP-1000 pulse wave unit (Nippon Colin Ltd, Komaki City, Japan) as described previously.[18,19] After an overnight fast and 5 min rest, PWV was measured from a supine position. Carotid and femoral artery pressure waveforms were recorded from multi-element tonometry sensors at the left carotid and the left femoral arteries. Brachial and tibial artery pressure waveforms were measured by an oscillometric method as described previously.[19] The electrocardiogram was monitored from electrodes on both wrists. Heart sound S1 and S2 were detected by a microphone on the left edge of the sternum at the third intercostal space. The waveform analyzer measures time intervals between S2 and the notch of the carotid pulse wave (Thc), and between the carotid and femoral artery pulse wave (Tcf). The sum of Thc and Tcf gives the time required for pulse waves to travel from the heart (aortic orifice) to the femoral artery (Thf). The hfPWV was calculated from the following equation: Lhf/(Thc + Tcf). Lhf is the distance from the heart to the femoral artery. The baPWV was calculated from the equation: D1-D2/T. D1 is the distance between the heart and ankle, D2 is the distance between the heart and brachium and T is the transit between the right brachial arterial wave and right tibial arterial wave. The dis-

tance between the sampling points and Lhf are automatically calculated from the patient height, and were divided by the time interval for the wave form from each measuring point.[18-20]

The baPWV, a central and peripheral stiffness index, and hfPWV, a central stiffness index, are being used as arterial stiffness markers, due to ease of measurement, reproducibility, and validity in previous studies.[19-21]

Statistical analysis

In this study, we categorized all the cases into three groups according to the level of ApoB/ApoA-I ratio. Results are expressed as the mean±SD. Comparisons of discrete variables were made using the chi-square method and independent t test was used for continuous variables. If the distribution was skewed, a non-parametric test was used.

In the multiple linear regression model, the variables that showed significant association ($P < 0.05$) in the simple univariate linear regression analysis and/or are known to effect indexes of arterial stiffness (hfPWV, baPWV) were entered into the model. In model 1, the entire population was used for analysis. In model 2, patients were divided according to the gender. Because of collinearity, triglyceride, HDL cholesterol and LDL cholesterol were not entered into the regression analysis. All statistical analysis was performed with SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Clinical characteristics

The baseline characteristics of the study population are shown in table 1. The average age of the study population was 55.9±10.1 years of age (range, 30 to 78) with 398 (60.7 %) being male. Because this was a tertiary care hospital recruited population cohort, the study group was a relatively high risk population with 290 (44.2%) patients having a history of coronary artery disease and 95(14.5%) patients having a history of diabetes mellitus (DM). The average ApoB level was 79.9±21.2 mg/dL and the average ApoAI level was 138.7±4.0 mg/dL. The average ApoB/ApoAI ratio was 0.60±0.19. The average hfPWV was 971±182 cm/sec and the average baPWV was 1462±232 cm/sec. All the patients were taking at least one class of antihypertensive drugs (Table 2) and 239 (36.4%) patients were taking statins at the time of testing. The baseline characterstics differed to some degree according to gender (Table 3). Males were significantly younger than the female population and had a significantly higher proportion of patients with history of coronary artery disease. The ApoB/ApoAI ratio was significantly lower in males due to the lower level of ApoAI. Significantly higher proportion of male patients was taking statins.

Table 1. Baseline characteristics of the study population

	N = 656
Age (years)	55.9 ± 10.1
Male (%)	398(60.7%)
Official BP SBP (mmHg) DBP (mmHg)	 127 ± 16 78 ± 11
Smoking (%)	309(47.1%)
CAD (%)	290(44.2%)
DM(%)	95(14.5%)
BMI (kg/m^2)	25.3 ± 3.0
T. chol (mg/dl)	183.7 ± 35.7
TG (mg/dl)	147.1 ± 92.4
HDL (mg/dl)	46.2 ± 14.4
LDL (mg/dl)	108.9 ± 34.1
ApoB(mg/dl)	79.9 ± 21.2
ApoAI(mg/dl)	138.7 ± 24.0
ApoB/AI ratio	0.60 ± 0.19
FBS (mg/dl)	94.7 ± 24.7
hfPWV (cm/sec)	971 ± 182
baPWV cm/sec)	1462 ± 232

Values are presented as n (%) or mean ±; SBP, systolic blood pressure; DBP, diastolic blood pressure;CAD, coronary artery disease; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBS, fasting blood sugar; hfPWV, heart to femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity.

Table 2. Antihypertensive and antihyperlipidemic medication history

	N = 656
ACE inhibitors (%)	115(17.5%)
ARB (%)	232(35.4%)
Beta blockers (%)	347(52.9%)
CCB (%)	381(58.1%)
Diuretics (%)	100(15.2%)
Statins (%)	239(36.4%)

Groups were classified according to tertiles; ACE, angiotensin-converting enzyme; ARB, angiotensin-converting enzyme receptor blocker; CCB, calcium channel blocker

Multiple linear regression

Multiple linear regression of the entire study group(Table

Table 3. Baseline characteristics of the study population according to gender

	Male(N=398)	Female(N=258)	P-value
Age (years)	54.6 ± 10.5	57.8 ± 9.0	< 0.001
Official BP			
SBP (mmHg)	127 ± 16	127 ± 16	0.868
DBP (mmHg)	79 ± 11	76 ± 10	< 0.001
Smoking (%)	297(74.6%)	12(4.7%)	< 0.001
CAD (%)	220(55.3%)	70(27.1%)	< 0.001
DM(%)	64(16.1%)	31(12.0%)	0.148
BMI (kg/m^2)	25.4 ± 2.7	25.1 ± 3.3	0.220
T. chol (mg/dl)	177.4 ± 33.8	193.3 ± 36.6	< 0.001
TG (mg/dl)	150.1 ± 91.3	142.5 ± 94.2	0.302
HDL (mg/dl)	44.5 ± 11.9	48.9 ± 17.2	< 0.001
LDL (mg/dl)	103.6 ± 31.8	117.0 ± 35.9	< 0.001
ApoB(mg/dl)	79.3 ± 20.7	80.8 ± 21.9	0.364
ApoAI(mg/dl)	134.3 ± 21.9	145.5 ± 25.6	<0.001
ApoB/AI ratio	0.61 ± 0.19	0.58 ± 0.19	0.037
FBS (mg/dl)	96.9 ± 26.2	91.3 ± 22.0	0.004
hfPWV (cm/sec)	984 ± 188	952 ± 171	0.028
baPWV cm/sec)	1444 ± 222	1490 ± 245	0.011
Statins	158(39.7%)	81(31.4%)	0.031

Values are presented as n (%) or mean ±; SBP, systolic blood pressure; DBP, diastolic blood pressure;CAD, coronary artery disease; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBS, fasting blood sugar; hfPWV, heart to femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity

Table 4. Multiple linear regression analysis for independent determinants of increased hfPWV and baPWV

	t	Standardized Coefficient	*P*-value
hfPWV (R^2 = 0.505)			
Age	19.3	0.564	< 0.001
Systolic BP	17.0	0.499	< 0.001
Male gender	4.02	0.155	<0.001
ApoB/ApoAI ratio	2.33	0.068	0.020
Heart rate	2.17	0.062	0.030
DM	2.12	0.060	0.034
BMI	-3.66	-1.06	< 0.001
Statin	0.856	0.025	0.392
Smoking	0.211	0.008	0.833
baPWV (R^2= 0.480)			
Age	14.7	0.440	< 0.001
Systolic BP	18.4.	0.554	< 0.001
Male gender	-1.86	-0.073	0.063
ApoB/ApoAI ratio	2.49	0.074	0.013
Heart rate	6.08	0.178	< 0.001
DM	1.54	0.045	0.124
BMI	-3.92	-0.117	< 0.001
Statin	0.31	0.009	0.756
Smoking	1.30	0.051	0.193

Hypertensive and lipid-lowering agents were controlled in this analysis.
hfPWV, heart to femoral pulse wave velocity; baPWV, brachial to ankle pulse wave velocity; BP, mean blood pressure; FBS, fasting blood sugar; BMI, body mass index

4) revealed that, after controlling for age, gender, systolic blood pressure, heart rate, DM, body mass index (BMI), statins and smoking, ApoB/ApoAI was significantly associated with both hfPWV (R^2 = 0.505, β = 0.068, P = 0.020) and baPWV. (R^2 = 0.480, β = 0.074, P = 0.013) Subgroup analysis(Table 5) revealed that the significant association of ApoB/ApoAI was significant only for the male population. [hfPWV(R^2 = 0.562, β = 0.108, P = 0.003) and baPWV (R^2 = 0.467, β = 0.104, P = 0.008)].

4. Discussion

In this study, we demonstrated a significant association of ApoB/ApoAI with baPWV and hfPWV in treated, male hypertension patients, after adjustment for confounding factors and medications. To our knowledge this is the first population study to demonstrate the significant association of ApoB/ApoAI in hypertension patients.

Although some studies have reported significant relationship of dyslidemia with arterial stiffness, the relationship is inconsistent.[10,12,22,23] Because high proportion of patients with hypertension are associated with normal to low LDL cholesterol with high triglyceride and low HDL cholesterol, the number of atherogenic particles and the antiatherogenic particles may have a stronger predictive value for cardiovascular disease. The level of LDL cholesterol may not always reflect the number of atherogenic particles in the circulation. This has been well demonstrated in several epidemiologic studies.[13-15] The increase in atherogenic particles may result in impaired bioavailability of nitric oxide with subsequent increase in oxidative stress and arterial stiffness.[22,24,25]

Studies have shown that ApoB/ApoAI ratio is more closely related with endothelial dependent vasodilation than LDL cholesterol.[24,26] Also, the deposition of atherogenic lipoproteins in the vessel wall may increase the collagen and calcium content resulting in increase of arterial stiff-

ness.[24,27]

The reason for the significant association of ApoB/ApoAI ratio in males and the lack of association in females is not clear at this time. The relatively higher ApoAI level, resulting in lower level of ApoB/ApoAI ratio and narrow range of values (0.15-1.22 in females compared to 0.20-1.64 in males) may be one of the factors influencing the lack of significant association in females. Estrogen is associated with enhancement of endothelial function with data showing significant reduction of central arterial stiffness with hormone replacement therapy.[28,29] The effect of estrogen on endothelial function may influence the effects of variables such as the ApoB/ApoAI ratio which effect arterial stiffness through modification of endothelial function. However, the fact that majority of women in this study population were post-menopausal (84.1% of women with age ≥50 years of age), may have confounded the analysis. We are limited by a lack of medical history regarding hormone replacement therapy in this group of patients.

Table 5. Multiple linear regression analysis for independent determinants of increased hfPWV and baPWV according to gender

Males	t	Standardized Coefficient	*P*-value
hfPWV (R^2 = 0.562)			
Age	17.5	0.623	< 0.001
Systolic BP	14.6	0.530	< 0.001
ApoB/ApoAI ratio	3.04	0.108	0.003
Heart rate	1.10	0.039	0.271
DM	2.21	0.075	0.028
BMI	-3.93	-0.138	< 0.001
Statin	1.49	0.053	0.138
Smoking	0.886	0.030	0.376
baPWV (R^2= 0.467)			
Age	9.96	0.391	< 0.001
Systolic BP	15.1.	0.605	< 0.001
ApoB/ApoAI ratio	2.65	0.104	0.008
Heart rate	3.03	0.117	0.003
DM	0.770	0.029	0.442
BMI	-5.83	-0.226	< 0.001
Statin	-0.513	-0.020	0.608
Smoking	1.80	0.068	0.073
Females	t	Standardized Coefficient	*P*-value
hfPWV (R^2 = 0.429)			
Age	8.72	0.449	< 0.001
Systolic BP	9.45	0.469	< 0.001
ApoB/ApoAI ratio	0.60	0.030	0.553
Heart rate	2.23	0.111	0.026
DM	0.53	0.026	0.596
BMI	-0.98	-0.051	0.326
Statin	-0.11	-0.006	0.910
Smoking	-1.34	-0.066	0.182
baPWV (R^2= 0.555)			
Age	10.9	0.494	< 0.001
Systolic BP	11.2	0.488	< 0.001
ApoB/ApoAI ratio	-0.058	-0.003	0.954
Heart rate	5.62	0.245	< 0.001
DM	1.43	0.062	0.155
BMI	-0.228	-0.010	0.820
Statin	0.211	0.010	0.833
Smoking	0.058	0.003	0.954

Although there are reports that aging has a greater influence in arterial stiffness in females,[30,31] this was not the case in this study which demonstrated a smaller standardized coefficient in females(Table 5).

Although thatl function atio which effect arterial stiffness thrureplacement therapy.A potential limitation of our study is that all the patients in this study were treated hypertension patients. Therefore, the long-term effect of anti-hypertensive medications on arterial stiffness cannot be ruled out as a confounding factor. Secondly, 239 (36.4%) patients were taking statins at the time of examination which may account for the relatively low value of ApoB/ApoAI ratio in this study. We tried to correct for this confounding factor by controlling for statin use in the multiple regression analysis. Thirdly, because the data was a cross sectional analysis, we could not assess the long term effects of higher ApoB/ApoAI ratio on the progression of arterial stiffness.

Fourthly, because this study was performed in a relatively high risk hypertension patients, the result cannot yet be generalized to the entire population. Further studies to demonstrate the association of ApoB/ApoAI ratio with arterial stiffness in the general population may be needed.

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