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Plasma Apolipoproteins and Lipids in Normal Persons and Patients with Hypertension

Seung Sei Lee, M.D., Young Man Jhoo, M.D., Dong Joo Oh, M.D.
Man Ho Lee, M.D., Eul Soon Chung, M.D. and Sang Jong Lee, M.D.

Department of Internal Medicine,
Koryo General Hospital, Seoul, Korea

We measured apolipoprotein A (ApoA), apolipoprotein B (ApoB), and lipid levels in 115 hypertensive patients and 100 normal subjects in order to evaluate the risk of atherosclerotic heart disease in hypertensive patients. The hypertensive patients were divided into the following subgroups: blood pressure controlled (A) and uncontrolled hypertensive subgroup (B), and without complication (C) and with complication (D).

In the hypertensive group, the mean plasma ApoA, ApoB, total cholesterol, triglyceride and beta-lipoprotein (LpB) levels were significantly higher than in the normal control group. The plasma high density lipoprotein cholesterol (HDL-cholesterol) level was not significantly different between the hypertensive group and the normal control group. ApoB/A ratio in the hypertensive group was higher than in the normal control group, but the difference was not significant statistically.

In the hypertensive subgroups, plasma Apo A was higher in all the hypertensive subgroups compared to normal control group, but these differences were not statistically significant. In subgroup B, C and D, the plasma ApoB level increased significantly as compared to the normal control group, but not so in the subgroup A. All of the subgroups had significantly higher levels of triglyceride and LpB level than the normal control group. HLD cholesteol level of all ot the subgroups did not show any significant difference as compared to the normal control group. In subgroup B, C and D, the ApoB/A ratio was not significantly different from the normal control group. In the subgroup A, ApoB/A ratio was lower than in the normal control group, this was not significant statistically. Between subgroup A and B, and subgroup C and D, all of the plasma lipids and apolipoproteins did not show significant differences.

Thus our results showed that ApoB, LpB and triglyceride, which are closely related to atherosclerotic heart disease, were significantly increased in any of hypertensive subgroups compared to the normal control group.

Key Words: *Apolipoprotein A, Apolipoprotein B, Hypertension*

INTRODUCTION

Hypertension is a major risk factor for the atherosclerotic vascular disease in coronary, cerebral, and peripheral arteries.[1-3] Examination of atherosclerotic lesions has revealed that each lesion contains significant amounts of three cellular elements: smooth muscle cell proliferation; large amounts of connective tissue matrix, including collagen, elastic fibers, and proteoglycans; and an accumulation of intracellular and extracellular lipid.[4] These atherosclerotic plaques arise because altered endothelial permeability allows certain reactive macromolecular plasma proteinsd (plansma low-density lipoproteins and fibrinogens, which are normally largely confined to the circulation) to penetrate endothelium and interact with charged

Address reprint requests: Sang Jong Lee, M.D. Department of Internal Medicine, Koryo General Hospital, Seoul, Korea

components of the connective tissue gel of the arterial wall or other tissues.[5] With recent advances in our knowlege of lipoprotein metabolism more insight has been gained into the role of hyperlipidemia as a risk factor. Apolipoprotein A (ApoA),[6,7] apolipoprotein B (ApoB),[8-11] and ApoB/A ratio, [12] especially, are now considered to be good discriminators of atherosclerosis as well as high-density lipoprotein cholesterol (HLD-cholesterol) and low-density lipoprotein (LDL).[13,14]

There have been several studies[16-24] on plasma lipid in the hypertensive patient, but few on apolipoproteins in the hypertensive patient, carried out in this country.

We measured the plasma ApoA and ApoB as well as the total cholesterol, triglyceride, HLD cholesterol, and beta-lipoprotein (LpB) in hypertensive patients and compared them with those of the normal subjects in the control group to see whether the risk indices for coronary artery disease are increased in hypertensive patients. We also tried to compare the plasma lipid and apolipoprotein levels between the blood pressure controlled and blood pressure uncontrolled subgroups, and between the patients with complications and those without complications.

MATERIALS AND METHODS

We studied 115 hypertensive patients, who visited or were admitted to internal medicine service at Koryo General Hospital and a control group of 100 normal subjects. In the hypertensive group, there were 68 men and 47 women, and in the control group, 52 men and 48 women. We divided the 115 hypertensive patients into subgroups, A and B, with "A" representing a blood pressure-controlled (systolic blood pressure under 160 mmHg and diastolic blood pressure under 95 mmHg) hypertensive subgroup, and with "B" representing uncontrolled (systolic blood pressure over 160 mmHg or diastolic blood pressure over 95 mmHg) hypertensive subgroup. Subgroup A included 16 patients, 8 males and 8 females, and subgroup B, 99 patients, 60 males and 39 females.

Then, we divided the same 115 hypertensive patients into subgroup C and subgroup D. Subgroup C included patients without complications according to a fundoscopic examination, a chest x-ray and an electrocardiogram, and subgroup D included those in whom at least one complication was found on the above tests: retinopathy on the fundoscopic examination, evidence of hypertensive cardiovascular disease or atherosclerotic heart disease on the chest X-ray, or strain, ischemia, or infarction on the 12-lead electrocardiogram. Subgroup C included 41 patients, 27 males and 14 females; and subgroup D included 74 patients, 41 males and 33 females.

Blood samples were taken in the morning after the subjects had fasted for 12 hours.

The plasma ApoA and ApoB levels were measured by the radial immunodiffusion method; total cholesterol and triglyceride levels by the enzyme method; HLD cholesterol by the heparin-Mn precipitation method; and LpB by the immunoturbidity method.

RESULTS

Plasma ApoA, ApoB, and Lipid Levels in the Normal Subjecte

The apolipoproteins and lipid values for men and women in the normal control group are shown in Table 1. Mean plasma ApoA and ApoB levels of the normal control group were 1.877 ± 0.447 and 1.272 ± 0.268 (gm/l) respectively. There were no significant differences between men and women. Mean plasma total cholesterol and HLD cholesterol levels in the normal control group were 183.8 ± 36.6 and 52.4 ± 12.2 (mg/dl), respectively. Those of the female control group were significantly higher than those of the male control group ($p<.05$, $p<.005$, respectivey). The mean plasma triglyceride level was 130.1 ± 57.7(mg/dl), and there were no significant differences between the male and the female control groups: The mean plasma LpB level was 395.6 ± 89.3 (mg/dl), and again, there were no significant differences between the male and the female control groups. The mean ApoB/A ratio and total cholesterol/HLD cholesterol ratio were 0.715 ± 0.236 a 3.667 ± 936. These ratios were higher in the male than in the female control group, but did not reach statistical significance. There was a positive correlation between ApoA and HDL cholesterol ($r=0.56$, $p<.005$). There were also strong positive correlations between ApoB and total cholesterol ($r=0.72$,$p<.005$), and ApoB and LpB ($r=0.67$, $p<.005$).

Comparison of the Hypertensive Patients with the Normal Subjects in the Control Group

Direct comparisons of apolipoprotein and lipid

values between the hypertensive and the control group are shown in Table 1.

The mean plasma ApoA level in the hypertensive group was 1.991±0.337 (gm/l), which was significantly higher ($p<.05$) than that in the control group. But the mean plasma HLD cholesterol level in the hypertensive group was 51.8±10.4 (mg/dl), which was similar to that of the control group.

The mean plasma ApoB, total cholesterol, and LpB levels in the hypertensive group were significantly higher compared with the levels in the control group (mean: 1.420±0.318 gm/l, 197.8±40.7 mg/dl, 468.3±135.1 mg/dl: $p<.005$, $p<.01$, $p>.005$, respectively).

The mean plasma triglyceride level in the hypertensive group was 193.1±115.5 (mg/dl), which was significantly higher than that in the control group ($p<.005$). The ApoB/A ratio in the hypertensive group was 0.737±0.212, which was not significantly different from that of the control group. The total cholesterol/HLD cholesterol ratio in the hypertensive group was 3.986±1.003, which was significantly higher than that in the control group ($p<.05$).

Comparison of the Hypertensive Subgroups with the Control Group

The comparisons of apolipoproteins and lipid levels between the hypertensive subgroups and the control group are summarized in Table 2.

In subgroup A, the mean plasma ApoA, ApoB, HLD cholelsterol, and total cholesterol levels and the total cholesterol/HLD cholesterol ratio were higher than those in the normal control group; these differences, however, were not significant. The mean plasma triglyceride and LpB levels were 211.6±142.7 (mg/dl) and 463.1±142.7 (mg/dl) which was significantly higher than those in the normal control group ($p<.005$, $p<.05$, respectively). The ApoB/A ratio was lower in subgroup A than in the control group, but still without significance.

In subgroup B, the mean plasma ApoA level was 1.437±0.326 (gm/l), and the total cholesterol 199.1±40.5 (mg/dl), triglyceride 190.1±111.1 (mg/dl), LpB level 469.1±134.5 (mg/dl) and the total cholesterol/HDL cholesterol ratio was 3.982±1.023. All of these levels were significantly higher than those in the control group ($p<.05$ or 0.005).

In subgroups C and D, the mean plasma ApoA levels were slightly higher than those in the normal cotrol group, but there were no significant differences between each subgroup and the control group. The mean plasma HLD cholesterol was similar to that of the control group. The mean plasma ApoB levels in subgroups C and D were significantly higher than those in the normal control group ($p<.005$). The mean plasma total cholesterol levels in subgroup D was significantly higher than in the control group ($p<.005$), but there was no significant difference between subgroup C and the control group. The mean plasma triglyceride and LpB levels in subgroups C and D were significantly higher than those in the control group ($p<.005$). In subgroups C and D, the ApoB/A ratio tended to be higher than that in the control group, without significance. The total cholesterol/HLD cholesterol ratio of subgroup D was significantly higher than that of the control group ($p<.05$), but not that of subgroup C.

Between subgroups A and B, and subgroups C and D there were no significant differences in all kinds of levels and ratios.

DISCUSSION

Hypertension is a main risk factor for the development of atherosclerosis.[1-3] The chief cause of the excess morbidity and mortality rate in the hypertensive subject is its increased propensity to atherosclerotic disease. When atherosclerosis has developed, treatment of hypertension alone may lower the incidence of stroke, but will have little effect on the mortality from coronary heart disease.[25] Antihypertensive agents, such as beta-adrenergic recepter blocker[26-30] and diuretics[31-34] may cause hyperlipidemia. ApoB,[8-11] LDL,[13-15] triglyceride,[35,36] and total cholesterol[13-15] are closely related to atherogenesis but ApoA I[6,7] and HLD cholesterol[37-39] are inversely related to it.

ApoA is the main apolipoprotein of HLD and the amino acid sequence of ApoA I and ApoA II are known.[40,41] ApoA I is an activator of lecithin: cholesterol acyltransferase (LCAT)[42,43] and acts as a protector against atherogenesis.

ApoB is a structure protein of chylomicron, VLDL, and LDL, and interacts with the LDL receptor of the peripheral cells such as the skin fibroblast, the intimal endothelial cells, and the smooth muscle cells of the arterial walls, as well as with the corresponding receptors of hepatocytes, and with LDL internalization and degradation.[44,45] Obviously, LDL is an important contributor to the atherogenetic process.

Table 1. Plasma Lipid and Apolipoprotein Concentrations in Hypertensive and Normal Control Groups (Mean±S.D.)

	Sex	Number of subjects	Age (years)	ApoA (gm/l)	ApoB (gm/l)	HLD-C[1] (mg/dl)	TC[2] (mg/dl)	TG[3] (mg/dl)	LpB[4] (mg/dl)	ApoB/A Ratio	TC/HLD[5] Ratio	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Control	M	52	46.1 ±11.6	1.825 ±0.473	1.252 ±0.253	48.3 ±9.7	177.5 ±29.8	138.3 ±59.1	397.0 ±18.8	0.722 ±0.231	3.809 ±0.935	121.9 ±18.1	82.2 ±6.8
	F	48	52.1 ±11.0	1.934 ±0.416	1.293 ±0.285	56.7## ±13.1	190.6# ±32.4	121.0 ±55.4	394.2 ± 86.6	0.708 ±0.245	3.511 ±0.918	122.4 ±12.3	78.4 ±8.2
	Total	100	49.0 ±11.6	1.878 ±0.448	1.272 ±0.268	52.4 ±12.2	183.8 ±31.6	130.1 ±57.7	395.6 ±89.3	0.715 ±0.236	3.667 ±0.934	122.2 ±15.9	80.4 ±7.7
Hypertension	M	68	54.2 ±12.5	1.927 ±0.320	1.421 ±0.330	50.6 ±10.4	198.5 ±43.0	197.0 ±110.0	475.8 ±126.8	0.756 ±0.208	4.042 ±0.969	161.5 ±19.7	99.9 ±12.2
	F	47	58.2 ±8.7	2.804# ±0.435	1.419 ±0.301	53.7 ±10.1	196.9 ±37.5	187.5 ±124.1	457.3 ±146.9	0.709 ±0.216	3.807 ±1.043	157.4 ±20.9	98.4 ±13.4
	Total	115	55.9 ±11.2	1.991* ±0.377	1.420*** ±0.318	51.8 ±10.4	197.8** ±40.7	193.1*** ±115.5	468.3*** ±135.1	0.737 ±0.212	3.536** ±1.003	159.9 ±20.2	99.3 ±12.6

1) High density lipoprotein cholesterol
2) Total cholesterol
3) Triglyceride
4) Beta-lipoprotein
5) Total cholesterol/HDL cholesterol ratio

#: $p<.01$
##: $p<.005$
(Between male and female group)
*: $p<.05$
**: $p<.01$
***: $p<.005$
(Between normal control and hypertensive group)

Table 2. Comparisons of Lipid and Apolipoprotein Concentrations between Hypertensive Subgroups (Mean±S.D.)

	Normal control	Hypertensive Subgroups			
		Controlled	Uncontrolled	Without complication	With complication
Number of subjects	100	16	99	41	74
Age (years)	49.0±11.6	55.4±13.1	55.9±11.0	50.9±11.9	58.6±9.8
ApoA (gm/l)	1.879±0.473	1.986±0.411	1.992±0.416	2.023±0.368	1.974±0.384
ApoB (gm/l)	1.272±0.268	1.318±0.246	1.437±0.326**	0.429±0.381**	1.416±0.279**
HDL-C[1] (mg/dl)	52.4±12.2	52.2±9.4	51.8±12.2	51.0±8.7	52.3±11.2
TC[2] (mg/dl)	183.8±31.6	190.3±42.3	199.1±40.5**	195.3±49.3	199.2±35.3**
TG[3] (mg/dl)	130.1±57.5	211.6±142.7**	190.1±111.1**	214.8±105.0**	181.1±119.9**
LpB[4] (mg/dl)	395.7±89.3	463.1±142.7*	469.1±134.5**	497.2±144.5**	452.2±127.7**
ApoB/A Ratio	0.715±0.236	0.697±0.238	0.743±0.208	0.726±0.222	0.743±0.207
TC/HDL-C Ratio[5]	3.667±0.934	3.723±-0.859	3.982±1.023*	3.917±1.050	3.962±0.982*

1) High density lipoprotein cholesterol
2) Total cholesterol
3) Triglyceride
4) Beta-lipoprotein
5) Total cholesterol/HDL cholesterol ratio

*: $p<.01$
**: $p<.005$
(Between each hypertensive subgroup and control group)

In our study the mean plasma ApoA level in the normal male and female control groups were 1.825±0.473 and 1.934±.416 (gm/l) and there were no significant differences between the groups. According to Curry et al.,[46] the mean plasma levels of ApoA I and ApoA II were 1.43±0.24 and 0.78±0.17, respectively, in men, and 1.46±0.78 and 0.41±0.46 (gm/l), respectively, in women, which were higher than our results in the control group. Assmann et al.[47] observed that the mean plasma levels of ApoA I and ApoA II were 1.13±0.016 and 0.35±0.38 in men, and 1.24±0.068 and 0.41±0.046 (gm/l) in women. Avogaro et al.[48] reported that the mean plasma ApoA I and ApoA II levels were 1.178±0.098 and 0.338±0.079 (gm/l). These results were lower than our results.

We observed that there was a positive correlation between ApoA and HLD cholesterol ($r=0.56$, $p<.005$) in the control group. In the hypertensive group and all of its subgroups, those subgroups with and without complications and the controlled and uncontrolled hypertensive subgroups, the mean plasma ApoA levels were higher than in the control group, but the differences did not reach statistical significance.

Our data showed that the mean plasma ApoB level in the control group was 1.252±0.253 (gm/l). Avogaro et al.[49] reported that the mean plasma ApoB level was 1.337±0.29 in men and 1.381±0.278 (gm/l) in women and Avogaro et al.[48] reported that the mean plasma ApoB level was 1.263±0.03 (gm/l) in the normal group. According to Curry et al.[46] mean plasma ApoB level was 1.07±0.22 in men and 0.9±0.2 (gm/l) in women, which was lower than our result in the control group. In the control group, there were positive correlations between ApoB and the total cholesterol ($r=0.723$, $p<.005$), and between ApoB and LpB ($r=0.67$, $p<.005$) in our study.

In the hypertensive group and in three of its subgroups (those subgroups with and without complications, and the subgroup of uncontrolled hypertensive patients) the mean plasma ApoB levels were significantly higher than those in the control group ($p<.005$), but not higher than those in the controlled hypertensive subgroup. No other data were available concerning the levels of the ApoA and ApoB relating to hypertension.

In this study, the mean plasma HLD cholesterol level in the normal control group was 52.4±12.2 (mg/dl), which was significantly higher in the female than in the male control group ($p<.005$). Lee et al.[17] and Yim et al.[18] observed that the mean plasma HLD cholesterol levels were 48.8±13.5 and 46.0±5.2 (mg/dl), respectively, which were lower than our results for the control group. According to Chung et al.[22] the mean plasma HLD cholesterol levels were 48.2±11.4 (mg/dl) in men and 52.4±13.2 in women, which were similar to our results. In the hypertensive group, the mean plasma HLD cholesterol level in our study was 51.8±10.4 (mg/dl), which was similar to that in the control group, which was in accord with the reports by Lee et al.[17] and Chung et al.[22]

We observed that the mean plasma total cholesterol level in the normal control group was 177.5±29.8 (mg/dl) and that women tended to have a higher total cholesterol level than men; this difference was not statistically significant, however. Lee et al.,[17] Yim et al.,[22] and Sohn et al.[23] reported that the mean plasma total cholesterol levels were 170.3±35.4, 172.1±23.3, and 172.2±78.9 (mg/dl), respectively, which results also represented no significant difference between that for the male and that for the female control groups. In the hypertensive group of our study the mean total plasma cholesterol level was significantly higher than that of the control group ($p<.01$). The hypertensive patients that Lee et al.,[17] Yim et al.,[18] Ryoo et al.,[20] and Sohn et al.[23] observed also had a significantly higher value for the total cholesterol level than their control group had. Our study showed that the hypertensive subgroup with complications and the uncontrolled hypertensive subgroup have significantly higher values of total cholesterol than the control groups, but the hypertensive subgroup without complications and the controlled hypertensive subgroup have not.

In our study, in the control group, the mean plasma triglyceride level was 130±57.7 (mg/dl), and men tended to have a higher value for the triglyceride level than women; this difference was not statistically significant, however. According to Sohn et al. [23] the mean plasma triglyceride level was 121.8±47.4, to Ryoo et al.,[20] 126.0±33.9, and to Lee et al.[17] 89.8±37.7 (mg/dl). Men also tended to have a higher value for the triglyceride level than women, in their studies.

In the hypertensive group, our data showed that the mean plasma triglyceride level was 190.1±111.1 (mg/dl), which was significantly higher than in the normal control group ($p<.005$). Lee et al.,[17] Ryoo et al.,[20] and Sohn et al.[23] also observed that hypertensive patients have a significantly higher value of triglyceride level than a control group.

We observed that all of the hypertensive subgroups: those subgroups with and without complications and the controlled and uncontrolled hypertensive subgroup had a significantly higher value for the triglyceride level than the normal control group ($p<.005$).

In the control group, the mean plasma LpB level that we obtained was 395.6 ± 89.3 (mg/dl) and there was no significant difference in the levels between the male and the female control groups. Ryoo et al.[20] and Sohn et al.[23] observed that the mean plasma LpB levels were 230.9 ± 43.5 and 424 ± 148.9 (mg/dl), which represented no significant difference between the male and the female control groups.

Our data showed that the mean plasma LpB level was 468.3 ± 135.1 (mg/dl) in the hypertensive group, which was significantly higher than that in the control group ($p<.005$). Sohn et al.,[23] observed that the hypertensive group also has a significantly higher LpB level than the control group, but according to Ryoo et al.[20] mean plasma LpB level was not significantly different between the control and the hypertensive groups. Our data showed that all of the hypertensive subgroups had significantly higher LpB levels than the control group ($p<.005$).

In the normal control group of our study the ratios of ApoB/A and total cholesterol/HLD cholesterol were 0.715 ± 0.236 and $3,667\pm0.394$ and there was no significant difference between those for men and those for women.

In the hypertensive group the ApoB/A ratio was 0.732 ± 0.212 which was higher than that in the control group. However it was without signifcance. The total cholesterol/HLD cholesterol ratio was 3.936 ± 1.003, which was significantly higher than that in the control group ($p<.05$). The total cholesterol/HLD cholesterol ratios in hypertensive subgroup with complications and the uncontrolled hypertensive subgroup were significantly higher than those in the control group but the other hypertensive subgroups provided no significant difference when compared with the control group.

Lipid metabolism in the hypertensive patient is not well understood at present, but several reports [29-34] shown that patients treated with beta-adrenergic blockers and/or diuretics may develop hyperlipidemia. The current publications in circulation dealing with the effects of beta-adrenergic receptor blockers on specific elements of lipid metabolism sometimes provide conflicting information.[26-30] It is most often reported that treatment with beta-blockers results in an elevation of the triglyceride level, while total cholesterol remains unchanged. Current discussion centers around the possibility of augmented resynthesis of triglycerides in the liver from the increased supply of free fatty acids. The increased supply of fatty acids is due to a mechanism of pronounced lipolysis, independent of catecholamines, which become active in response to the inhibition of catecholamine-induced lipolysis.[30]

The finding that diuretics induce changes in the levels of plasma lipids and lipoproteins an element of contradiction as well. Diuretic-induced elevation of LDL cholesterol as well as VLDL triglyceride has been reported, while HDL cholesterol, on the other hand, appears to be essentially unaffected by diuretics. The underlying cause of the increase in LDL remains unclear. Inas much as in the studies we are referring the reader to, there were no indications that hepatic lipoprotein synthesis increased or that VLDL underwent degradation, the possibility of hemoconcentration being caused by diuretics may be excluded with some certainty, in that the rise in LDL is attributed to a reduction of LDL catabolism.[31-34]

In our study the mean plasma HDL cholesterol was not ; significantly different between the hypertensive group and the control group. The mean total cholesterol level was elevated significantly in the hypertensive patients with the exception of those in the subgroup without complications and controlled hypertensive subgroup. ApoB, LpB, and triglyceride were significantly higher in the hypertensive patients in general, even those in the subgroup without complications and those whose hypertension was controlled, than in the normal subjects. However the ApoB/A and total cholesterol/HDL cholesterol ratios were variable. Further studies evaluating apolipoproteins and lipids in the hypertensive patient are needed.

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