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Coronary Sclerosis Risk Factors in Males with Special Reference to Lipoproteins and Apoproteins: Establishing an Index

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ABSTRACT

In order to ascertain the most effective index for predicting coronary sclerosis, the concentration of lipids, lipoproteins, and apoproteins in serum were determined in 45 males aged over 44 with angiographically diagnosed effort angina and in 153 male controls aged over 44 without ischemic heart disease (IHD) on physical examination. The results of our study are summarized as follows.

1) Alcohol intake of 25 g/day or more and smoking of 20 cigarettes/day or more showed significant odds ratios of 0.47 and 2.33, respectively.

2) By decrease of 10 mg/dl in HDLC level or of 10 mg/dl in Apo-AI level, the possibility of coronary sclerosis increases twofold after adjusting the effects of confounders.

3) LDLC/HDLC and Apo-B/Apo-AI are effective indices for predicting coronary sclerosis and, in particular, the probability of coronary sclerosis increases 3.8 times by increase of 0.5 in Apo-B/Apo-AI.

Key words: *Lipoproteins, Apoproteins, Multiple logistic regression, Odds ratio*

Hyperlipidemia, hypertension, smoking, and obesity are known to be risk factors in ischemic heart disease (IHD)[2,9,12]. Measurement of the components of lipoproteins and apoproteins in particular has become simplified. Low density lipoprotein cholesterol (LDLC) has been found to be an atherogenic factor[8,13] and high density lipoprotein cholesterol (HDLC) to be a protective factor of atherosclerosis[7]. However, there is a paucity of studies which quantitatively analyze the level of lipids, lipoproteins and apoproteins as risk factors of coronary atherosclerosis in conjunction with other risk factors[3,14]. We therefore confined our subjects to male effort angina patients with distinct stenosis diagnosed by coronary arteriography and to males found on physical examination not to have IHD as controls. A case-control study was conducted and the clinical significance of lipids, lipoproteins, and apoproteins as risk factors was quantitatively evaluated.

MATERIALS AND METHODS

The subjects in this study were 45 males aged over 44 diagnosed by coronary arteriography to have distinct stenosis of more than 25% without spasm and 153 male controls aged over 44 who were found not to have IHD in the physical exami-

nation of the present and former employees of Hiroshima University. Myocardial infarction patients and spastic angina patients were excluded because many patients with myocardial infarction die and spastic angina is little related to atherosclerotic changes. A survey was made of their daily smoking habit (more than 20 cigarettes/day or not), alcohol intake (more than 25 g/day or not) calculated in terms of ethanol involvement, and obesity index calculated by the modified method of Broca-Katsura using height and weight. Fasting blood was drawn from each subject early in the morning before food intake. Determination of serum total cholesterol (TC) and serum triglyceride (TG) was made by the enzymatic method, that of HDLC by dextran sulfate-magnesium chloride precipitation technique, and that of six types of apoproteins (Apo-AI, Apo-AII, Apo-B, Apo-CII, Apo-CIII and Apo-E) by single radial immunodifusion method (SRID). LDLC was determined by Friedewald's method[6].

Median, 25 percentile and 75 percentile of the distribution of lipids, lipoproteins, apoproteins and atherogenic indices (LDLC/HDLC and Apo-B/Apo-AI) were calculated. The difference between cases and controls was examined by Mann-Whitney U test. Odds ratio and box plots[10] were conducted to ascertain the differences in background factors such

as alcohol intake, smoking, age, fasting blood sugar (FBS) level and obesity index (OI). In order to adjust the background factors and to quantitatively estimate the level of lipids, lipoproteins, apoproteins and their ratios as risk factors of coronary sclerosis, multiple logistic regression was conducted.

RESULTS

1) Distribution of serum lipids, lipoproteins, apoproteins and their ratios

Table 1 shows the median, 25 percentile and 75 percentile of the distribution of various parameters in the cases and controls. Significant difference between the cases and controls was shown by Mann-Whitney U test in HDLC, Apo-AI, Apo-AII, Apo-B, LDLC/HDLC and Apo-B/Apo-AI, but no significant difference could be observed in TC, TG, LDLC and others.

2) Difference in background factors between the cases and controls

Alcohol intake of 25 g or more per day and smoking of 20 or more cigarettes per day revealed a significant difference in odds ratios (Table 2). The

Table 1. Median, 25 percentile and 75 percentile of the distribution of lipids, lipoproteins, apoproteins, and atherogenic indices in the cases and controls.

		Cases			Controls			Probability*
TC	mg/dl	217	(188	−249)	209	(186	−237)	0.39
TG	mg/dl	122	(101	−160)	115	(89	−143)	0.15
HDLC	mg/dl	41	(33	− 50)	49	(42	− 61)	<0.01
LDLC	mg/dl	145	(123	−170)	129	(108	−159)	0.07
Apo-AI	mg/dl	103	(91	−118)	138	(124	−154)	<0.01
Apo-AII	mg/dl	24	(22	− 29)	32	(28	− 35)	<0.01
Apo-B	mg/dl	109	(99	−136)	104	(92	−120)	0.05
Apo-CII	mg/dl	4.0 (	3.1−	4.9)	3.5 (	2.5−	4.6)	0.12
Apo-CIII	mg/dl	8.4 (	6.6−	9.8)	7.6 (	6.0−	9.6)	0.25
Apo-E	mg/dl	4.3 (	3.3−	5.0)	4.0 (	3.3−	4.9)	0.74
LDLC/HDLC		3.5 (	2.9−	4.1)	2.7 (	2.0−	3.4)	<0.01
Apo-B/Apo-AI		1.1 (	0.9−	1.3)	0.8 (	0.6−	0.9)	<0.01

*: Mann-Whitney U test

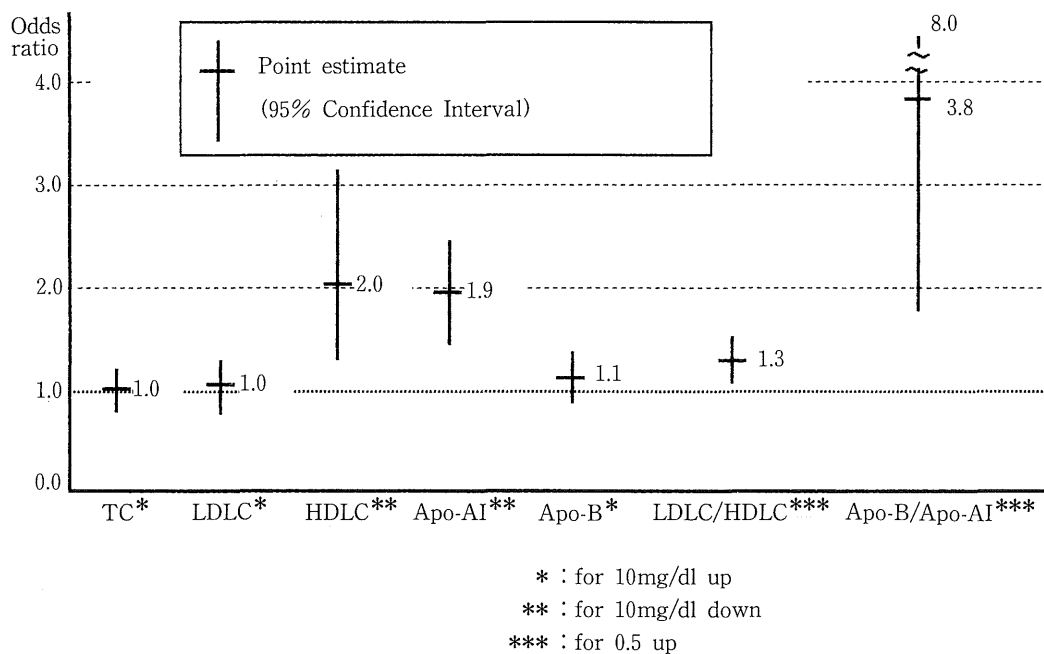**Table 2.** The effects of alcohol intake and smoking on IHD.

	Cases	Controls	Odds ratio	95% C. I.*
Alcohol intake				
≧25 g/day	13	71	0.47	0.23−0.96
<25 g/day	32	82		
Cigarette smoking				
≧20/day	27	60		
<20/day	18	93	2.33	1.18−4.59

*: 95% Confidence Interval
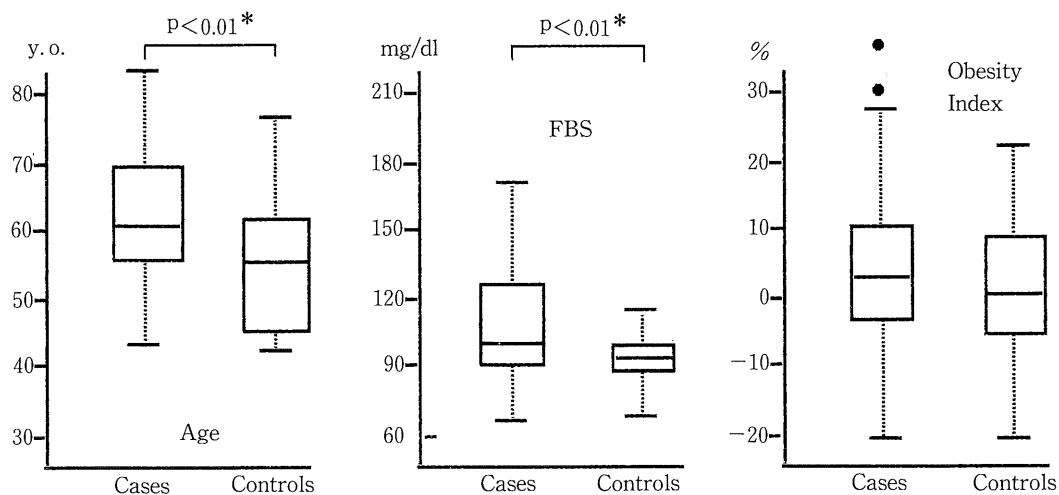
* : Mann-Whitney U test

Fig. 1. Difference in background factors between cases and controls. Difference in age and FBS level is significant.

Fig. 2. The odds ratios of various parameters after adjusting the confounders by multiple logistic regression. Odds ratios of HDLC, Apo-AI, and Apo-B/Apo-AI are significant.

probability of coronary sclerosis is, therefore, more than twofold higher in men who smoked 20 or more cigarettes per day than men who smoked less than 20 per day. The point estimate of odds ratio was 2.33. But the probability of coronary sclerosis is lower in man who drink alcohol 25 g or more per day than man who drink less than 20 g/day. The point estimate of odds ratio was 0.47. The difference in age and serum FBS levels between the cases and controls become evident with the use of box plots. There was, however, no significant difference in OI between the cases and controls (Fig. 1).

3) Odds ratios of various parameters for predicting coronary sclerosis

After adjusting the other significant factors (alcohol intake, smoking, age, and FBS levels), multiple logistic regression was conducted in order to estimate the level of risk factors of coronary sclerosis (Fig. 2).

The odd ratios of TC, LDLC, and Apo-B were not significant. These confidence intervals included 1.0 level as the odds ratio. But those of HDLC and Apo-AI were found to be significant. With a decrease of 10 mg/dl in HDLC level or 10 mg/dl in Apo-AI level, the possibility of coronary sclerosis increases approximately twofold after adjusting the effects of confounders. The odds ratios of LDLC/HDLC and Apo-B/Apo-AI were significantly high: 1.3 and 3.8 respectively. Because the odds ratio is in close agreement with relative risk, the possibility of coronary sclerosis increases 1.3 times by an increase of 0.5 in LDLC/HDLC. The possibility of coronary sclerosis increases 3.8 times with an increase of 0.5 in Apo-B/Apo-AI after adjusting the effects of confounders.

DISCUSSION

HDLC has attracted much interest as a protective factor against atherosclerosis, but there are reports[1] indicating that HDLC has no relation to the severity of IHD by coronary arteriography. Regarding atherosclerotic factors, interest has focused recently on apoproteins as components of lipoproteins. Apo-AI, Apo-AII, and Apo-B as apoproteins of lipoproteins have been extensively measured and examined for their possible significance[11,15]. Recently, subtypes of Apo-E have been determined and the significance of this index has been discussed[5,16]. But there is no evidence that the difference of subtypes of Apo-E is clearly concerned with the progress of atherosclerosis.

In evaluating risk factors, confounders such as age, sex, smoking, drinking and obesity should be taken into account and selective biases must be excluded. In the present study, the subjects were therefore restricted to males aged over 44 diagnosed by coronary arteriography to have effort angina. Myocardial infarction cases were excluded because, owing to death, they tend to drop out before the examination. Spastic angina cases were also excluded because they have little direct relationship to atherosclerosis. If these cases were included in the study, selective biases would develop.

Using box plots and odds ratio, in close agreement with relative risk, the difference in such background factors as age, serum FBS, smoking, and alcohol intake became apparent. To adjust these confounders, multiple logistic regression[4] was performed.

Even after adjusting the effects of confounders,

odds ratios of HDLC and Apo-AI remained significant. LDLC/HDLC and Apo-B/Apo-AI were found to be effective indices of atherosclerosis even after adjusting the other confounders. In particular, Apo-B/Apo-AI emerges as the best index for monitoring patients for the prevention of coronary sclerosis and in the screening of IHD patients.

REFERENCES

1. **Barboriak, J. J., Rima, A. A., Anderson, A. A., Schmid, H. M. and Tristani, F. E.** 1977. Coronary arterial occlusion and alcohol intake. Br. Heart. J. **38**: 289–293.

2. **Castelli, W. P.** 1984. Epidemiology of coronary heart disease: The Framingham study. Am. J. Med. **27**: 4–12.

3. **Connor, E. B., Suarez, V., Khaw, K. T., Criqui, M. H. and Wingard, D. L.** 1984. Ischemic heart disease risk factors after age 50. J. Chron. Dis. **37**: 903–908.

4. **Cox, D. D.** 1970. The analysis of binary data, Chapman and Hall, London.

5. **Dvignon, J., Gregg, R. E. and Sing, C. F.** 1988. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis **8**: 1–21.

6. **Fredrickson, D. S.** 1972. Estimation of the concentration of low-density-lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. **18**: 499–502.

7. **Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B. and Dawter, T. R.** 1977. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. Am. J. Med. **62**: 707–714.

8. **Jenkins, P. J., Horper, R. W. and Nestel, P. J.** 1978. Severity of coronary atherosclerosis related to lipoprotein concentration. British Med. J. **5**: 388–391.

9. **Kannel, W. B., Castelli, W. P., Gordon, T. and MacNamara, P. M.** 1971. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. Ann. Int. Med. **74**: 1–12.

10. **Kawanishi, M., Nakamoto, A., Hiraoka, M., Kuroki, Y., Itoh, M., Takata, K., Horiuchi, I., Konemori, G., Amioka, H., Matsuura, H. and Kajiyama, G.** 1989. Indices for prediction of coronary sclerosis with particular reference to Apo-B/Apo-AI ratio. J. Jpn. Atheroscler. Soc. **17**: 939–947.

11. **Noma, A., Yokosuka, T. and Kitamura, K.** 1983. Plasma lipids and apoproteins as discriminators for presence and severity of angiographically defined coronary artery disease. Atherosclerosis **49**: 1–7.

12. **The Pooling Project Research Group.** 1978. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the pooling project. J. Chron. Dis. **31**: 201–306.

13. **Tracy, R. E., Dzoga, K. R. and Wissler, R. W.** 1965. Sequestration of serum low-density lipoproteins in the arterial intima by complex formation. Proc. Soc. Exp. Biol. Med. **118**: 1905–1908.

14. **Truett, J., Cornfield, J. and Kannel, W.** 1967. A multivariate analysis of the risk of coronary heart disease in Framingham. J. Chron. Dis. **20**: 511–524.

15. **Vergani, C., Trovato, G. and Dioguardi, N.** 1978. Serum total lipids, lipoproteins cholesterol, apoproteins A and B in cardiovascular disease. Clin. Chim. Acta **87**: 127–133.

16. **Wardell, M. R., Brennan, S. O., Janus, E. D., Fraser, R. and Carrell, R. W.** 1987. Apolipoprpotein E2-Christchurch (136Arg->Ser): new variant of human apoplipoprotein E in a patient with type III hyperlipoproteinemia. J. Clin. Invest. **80**: 483–490.