Study on Lipid and Glucose Metabolism in Patients with Vasospastic Angina

Hisashi Yoshida, Keiji Murakami and Goro Mimura

The primary purpose of the present study was to evaluate the role of lipid and glucose metabolism in vasospastic angina. A group of 93 patients in whom the presence of ischemic heart disease was suggested, were classified into the control (C) group, consisting of 30 patients; the coronary artery disease (CAD) group, consisting of 47 patients; and the vasospastic angina (VSA) group, consisting of 16 patients. Among these three groups, age, total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), atherogenic index (AI), apolipoproteins and the prevalence of diabetes mellitus were compared. No age difference was seen among the three groups. The TC was the highest in the CAD group, followed by the VSA and C groups. A significant difference in TC was noted between the C and CAD groups and the C and VSA groups. TG levels were higher in the CAD group than in the C and VSA groups, without a significant difference among the three groups. The AI was significantly higher in the CAD group than in the C and VSA groups. No significant difference was noted in the prevalence of diabetes mellitus among the three groups. Apolipoprotein A-I (apo A-I) levels were higher in the VSA group than in the C and CAD groups, and the difference between the VSA and CAD groups was significant. Apolipoprotein A-II (apo A-II) levels were significantly higher in the VSA group than in the C and CAD groups. Although no significant difference was demonstrated in HDL-C levels in the present study, apo A-II levels were significantly higher in the VSA group, suggesting the presence of lipid metabolism abnormalities, including qualitative abnormalities of HDL in VSA.

Key words: Vasospastic angina, Coronary artery disease, Lipid metabolism, HDL-cholesterol, Apolipoprotein

There are many reports which discuss various viewpoints regarding risk factors for ischemic heart disease. Metabolic factors related to lipid and glucose metabolism have been studied in detail (5-16). Only a small number of studies, however, have examined lipid and glucose metabolism as risk factors for vasospastic angina (VSA) (1-4) and few reports are found which explore the role of apolipoprotein in this disorder. At the present time, the importance of coronary vasospasm in the pathogenesis of angina pectoris and myocardial infarction has been pointed out based on the progress of diagnostic techniques for ischemic heart disease. It is now important to evaluate the potential risk factors for VSA.

In order to elucidate the relationship between coronary vasospasm and the metabolism of lipids and glucose, lipid and glucose metabolism was studied in patients with VSA who underwent coronary arteriography. Lipid and glucose metabolic parameters were compared between a group with arteriography-demonstrated atherosclerotic heart disease and a control group.

MATERIALS AND METHODS

This study was conducted on 93 patients diagnosed to possibly be organic stenosis and/or coronary vasospasm patients. We performed coronary arteriography on them, along with an evaluation using a 75 g glucose tolerance test (GTT)
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and apolipoprotein determination. The patients were classified by diagnosis into a control (C) group with neither organic stenosis nor coronary vasospasm, coronary artery disease (CAD) group with old myocardial infarction or effort angina in the presence of significant coronary artery stenosis (more than 75%), and VSA group without 75% coronary artery stenosis and ST elevation in electrocardiograms (ECGs) taken during attacks of spontaneous chest pain and induction of coronary vasospasm with ergonovine loading. The ergonovine test was performed in the cardiac catheterization laboratory as heart rate and arterial blood pressure were continuously monitored. A standard 12 leads ECG was also recorded using radiolucent carbon fiber electrodes. Nitroglycerin was available for intracoronary administration. Ergonovine was administered intravenously as a bolus injection of 0.05 mg every 3 minutes until induction of typical angina or up to a maximal total dose 0.4 mg. Unless there was an ECG change (ST segment elevation) and/or symptoms (anginal pain) within 3 minutes after administration, the next dose of ergonovine was administered. When either anginal pain or ST segment elevation of greater than 1 mm compared with the control ECG was recognized within 3 minutes after ergonovine administration, coronary arteriography was taken. If coronary arteriography revealed total or subtotal vasospastic obstruction in proximal portions of coronary arteries, the ergonovine test was terminated and the patient classified positive. An intravenous bolus dose of 0.1-0.2 mg of nitroglycerin was administered as soon as possible. The test was also terminated when the maximal dose of ergonovine (0.4 mg) did not cause an ECG change or symptoms and the patient was classified negative. In our study, the mean degree of stenosis in the VSA group was 17.1 ± 4.4% (mean ± SEM). Patients with acute myocardial infarction and unstable angina were excluded.

The C, CAD and VSA groups contained 30 (16 males and 14 females), 47 (36 males and 11 females) and 16 (10 males and 6 females) patients, respectively, with mean ages of 56.4 ± 1.6, 58.0 ± 1.1 and 55.1 ± 2.7 years in each group, respectively (Table 1). Among these three groups, the mean age, serum total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), atherogenic index (AI), apolipoprotein A-I (apo A-I), A-II, B, C-II, E and the prevalence of diabetes mellitus were compared. Serum lipid measurements were performed on blood samples obtained in the early morning after an overnight fast. TC and TG were measured using an autoanalyzer based on an enzymatic method. HDL-C was measured with an enzymatic method after fractionation using dextran magnesium sulfate. The AI was calculated using the formula (TC — HDL-C)/HDL-C. Apolipoprotein was measured using a commercially available kit (Dai-ichi Kagaku) based on a single radial immunodiffusion (SRID) method. A diagnosis of diabetes mellitus was made based on the result of a 75 g GTT according to the WHO criteria.

The results were analyzed by the unpaired Student's t-test and Chi-squared test, employing p< 0.05 as the level of significance. All values were expressed as mean ± SEM.

RESULTS

The mean age was not significantly different among the three groups. The influence of age on the presence of atherosclerosis therefore appears to be negligible in this study.

Figure 1 shows the comparison of TC, TG, HDL-C, and AI among the three groups. TC levels were 182.4 ± 5.1, 238.3 ± 10.1 and 214.9 ± 11.4 in the C, CAD, and VSA groups, respectively. (The same group order is used for subsequent figures). The value was highest in the CAD group, followed by the VSA and C groups in decreasing order. The

Table 1. Subject

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<tr>
<th>1. Control (C) group</th>
<th>number 30 (male 16, female 14)</th>
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<td>age</td>
<td>56.4 ± 1.6</td>
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<th>2. Coronary artery disease (CAD) group</th>
<th>number 47 (male 36, female 11)</th>
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<td>age</td>
<td>58.0 ± 1.1</td>
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<th>3. Vasospastic angina (VSA) group</th>
<th>number 16 (male 10, female 6)</th>
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<td>age</td>
<td>55.1 ± 2.7</td>
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value was significantly lower in the C group than in the CAD and VSA groups. No significant difference was noted between the CAD and VSA groups. TG levels were 182.1 ± 18.7, 210.2 ± 27.9 and 171.8 ± 24.1, respectively. The CAD group tended to have higher values than the C and VSA groups, but no significant difference was noted among the three groups. HDL-C levels were 44.8 ± 2.0, 42.6 ± 1.7 and 47.7 ± 3.1, respectively. The CAD group tended to have lower values than the C and VSA groups, but no significant difference was noted among the three groups. The AI was 3.3 ±
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0.2, 4.9 ± 0.3 and 3.7 ± 0.3, respectively. The CAD group had significantly higher values than the C and VSA groups.

Figure 2 compares the apolipoprotein values among the three groups. Apo A-I levels were 142.2 ± 4.5, 116.4 ± 3.6 and 150.5 ± 7.2, respectively. The C and VSA groups showed significantly higher values than the CAD group. Between the C and VSA

| Table 2. Serum levels of TC, TG, HDL-C, AI, Apolipoproteins and prevalence of diabetes mellitus (DM) in three groups |
|-----------------|-----------------|-----------------|
|                 | C group          | CAD group        | VSA group        |
| TC               | 182.4 ± 5.1      | 238.3 ± 10.1**   | 214.9 ± 11.4**   |
| TG               | 182.1 ± 18.7     | 210.2 ± 27.9     | 171.8 ± 24.1     |
| HDL-C            | 44.8 ± 2.0       | 42.6 ± 1.7       | 47.7 ± 3.1       |
| AI               | 3.3 ± 0.2        | 4.9 ± 0.3**      | 3.7 ± 0.3#       |
| Apo A-I          | 142.2 ± 4.5      | 116.4 ± 3.6**    | 150.5 ± 7.2##    |
| Apo A-II         | 29.7 ± 1.1       | 27.7 ± 1.2       | 34.3 ± 2.1#####  |
| Apo B            | 102.7 ± 3.7      | 98.3 ± 8.3       | 94.6 ± 10.7      |
| Apo C-II         | 4.3 ± 0.3        | 4.9 ± 0.4        | 4.6 ± 0.4        |
| Apo E            | 5.1 ± 0.3        | 4.8 ± 0.4        | 5.2 ± 0.2        |
| DM (%)           | 16.7             | 23.4             | 12.5             |

C = control; CAD = coronary artery disease; VSA = vasospastic angina. Each value represents the Mean ± SEM. Significantly different from the control value at *P<0.05 and **P<0.01. Significantly different from the value of CAD at #P<0.05 and ##P<0.01.

The prevalence of diabetes mellitus was 16.7%, 23.4% and 12.5% in the three groups, respectively, without significant difference (Fig. 3).

DISCUSSION

Many reports have discussed the risk factors for ischemic heart disease, including the Framingham study reports. The main risk factors include hypercholesterolemia, smoking, hypertension, obesity and diabetes mellitus. In recent years, the importance of coronary vasospasm in ischemic heart disease has been recognized, arousing interest in VSA due to coronary vasospasm. Only a small number of reports are available regarding the risk factors for VSA (1-4). Few reports have explored the relationship between VSA and apolipoprotein levels until the present study.

The greatest risk factor for coronary atherosclerosis is hypercholesterolemia, and an intimate correlation was found between TC and the incidence of CAD in the Framingham study (5) and the Pooling Project (6). Scholl et al. (4) reported higher TC values in VSA with coronary arterial lesions than in normal controls. In our results, TC was significantly higher in CAD and VSA than C, in agreement with the previous reports.

Opinions have been divided as to whether TG alone may be a coronary risk factor. According to the reports of Castelli et al. (7), the Framingham study (8) and Hulley et al. (9), it has not been shown to be a risk factor. Carlson et al. (10), however, pointed out the role of TG as an independent risk factor in Stockholm prospective study. At the present time, no definite conclusion has been reached regarding this problem. In our results, TG levels tended to be higher in the CAD group than in the C and VSA groups, but no significant difference was noted among the three groups.

The relationship between a decrease in HDL-C levels and the occurrence of ischemic heart disease
was reported in 1951 (11). Since the report of Miller et al. (12) regarding the significantly decreased levels of HDL-C in patients with ischemic heart disease in 1975, attention has been focused on the significance of evaluated HDL-C levels as a negative risk factor. The Framingham study in 1977 (13) led to the recognition of HDL-C as the most important negative risk factor in ischemic heart disease. Although the anti-atherosclerotic mechanism of HDL has not been completely elucidated, HDL acts as lecithin: cholesterol acyltransferase (LCAT) to esterify free cholesterol in the peripheral tissues and transport it to the liver in a reverse cholesterol transport. This may result in an anti-atherosclerotic action. In the present study, HDL-C levels were not significantly different among the three groups, but the CAD group tended to have lower values than the C and VSA groups in agreement with the previous reports.

AI was calculated using the formula (TC — HDL-C)/HDL-C, TC — HDL-C probably reflects LDL-C. AI thus reflects both LDL-C and HDL-C, each representing an independent risk factor. AI is thought to be an extremely effective index for coronary atherosclerosis. According to our results, the AI was the highest in the CAD group, followed by the VSA and C groups in decreasing order. The value in the CAD group was significantly higher than in the two other groups, in accordance with previous reports. No significant difference was found between levels in the C and VSA groups.

Diabetes mellitus is, no doubt, one of the risk factors for CAD, according to the results of epidemiological and clinical studies. The prevalence of diabetes mellitus in patients with CAD was 12% according to Conrad (14) and 15% according to Datey et al. (15). In order to accurately determine the frequency of diabetes mellitus among patients with CAD, a GTT is necessary. According to Jakobson et al. (16), impaired glucose tolerance was noted in 53.6% of patients with CAD and 25.8% of control subjects. In our results, the frequency of diabetes mellitus was the highest in the CAD group at 23.4%, followed by the C group at 16.7% and the VSA group at 12.5%. No significant difference was noted among the three groups. In VSA, the role of diabetes mellitus as a risk factor does not seem to be as important as in CAD.

Roheim et al. (17) in 1965 called the protein portion of lipoprotein apolipoprotein. This was followed by discovery of various apolipoproteins. The major apolipoproteins known at present include apo A-I, A-II, B, C-II, C-III, D, E. Each of these is present in some lipoprotein at a specific concentration and plays a unique function.

Albers et al. (18) measured apo A-I in 24 patients with myocardial infarction with low levels of HDL-C. Like HDL-C, a significantly lower value of apo A-I was found. Other reports also describe a low levels of apo A-I along with HDL-C in patients with CAD (19-21). Like apo A-I, apo A-II levels were also significantly lower in CAD (19-21).

Vander Heiden et al. (22) compared coronary arteriographic findings and lipoprotein or apolipoprotein levels. Apo B was found to most accurately reflect the degree of severity of the coronary arterial lesion. According to the consensus of the reports of various investigations, apo B values increase along with high LDL values (19-21, 23).

While the mechanism of such a fall in apo A-I and A-II levels and the rise of apo B, and their relationship with the process of coronary atherosclerosis remains unknown, these change are also noted in normolipidemic patients with CAD, and appear to be quite useful in the diagnosis of coronary atherosclerosis.

According to our results, apo A-I was significantly lower in the CAD group than in the C group, and apo A-II also tended to be lower in comparison with the C group, although the difference was not significant. This is in agreement with the reports by various investigators. Apo B levels showed no significant difference among the three groups.

In the VSA group, apo A-I levels tended to be high compared with the C group, although without a significant difference, and apo A-II levels were significantly higher in the VSA group than in the C and CAD groups. Apo A-I and A-II are the main structural proteins of HDL, as previously described. In the present study, apo A-I and A-II levels tended to be high despite the absence of a significant difference in HDL-C among the three groups. This suggests the presence of lipid metabolism abnormalities, including qualitative abnormalities of HDL, in the VSA group. While the correlation between HDL-C changes and changes of apo A-I
and A-II levels was relatively high, an absence of correlation was also reported in some patients with hypertriglyceridemia. Harano et al. reported the rise of apo A-I and A-II in non insulin dependent diabetes mellitus (NIDDM) despite the tendency of HDL-C to fall. No such dissociation between HDL-C and apo A-I or A-II levels has been reported in patients with VSA. No significant difference was found in apo C-II and E levels among the three groups.

The lipid and glucose metabolism in the three groups were compared based on these results. In attempting to correlate VSA and lipid metabolism, the relationship between coronary vasospasm and coronary atherosclerosis has attracted the most intense attention. The possibility of an important role of coronary atherosclerosis in the etiology of coronary vasospasm has been repeatedly suggested based on studies in experimental animals. Shimokawa et al. (24) produced localized intimal thickening in Göttingen strain minipigs by feeding a high cholesterol diet after abrading the intima of the coronary artery with a balloon catheter. These investigators then successfully induced coronary arterial spasm at the site of intimal thickening with histamine and serotonin. Kawachi et al. (25) induced localized coronary atherosclerosis in dogs using a balloon catheter, and subsequently induced coronary vasospasm in response to ergonovine loading. They observed no significant coronary artery stenosis at the site of spasm according to the coronary arteriography, but demonstrated initial stage atherosclerotic lesions at the same site histologically. This strongly implies a relationship between atherosclerosis and vasospasm. Yokoyama et al. (26) considered that an increase in cholesterol in the cell membranes at an early stage of atherosclerosis alters ion permeability in the cell membrane which, in turn, influences the contraction of the vascular smooth muscle. What these reports uniformly suggest is the ready occurrence of spasm at a site where an initial atherosclerotic lesion is present or where coronary atherosclerosis is mild. In fact, coronary arteriography has been reported to disclose mild stenosis or absence of organic change in patients with VSA (27, 28) and similar reports have been increasing in number in recent years.

In our results, the apo A-I levels were found to be significantly higher in patients with VSA than in patients with CAD. Since apo A-I acts as a potentiating factors for LCAT, it may play a significant role in the anti-atherosclerotic action of HDL. Although a direct causal relationship between these results and mild organic coronary artery stenosis in VSA still remains to be demonstrated, some relationship is suggested.

In the VSA group, apo A-II levels were also significantly higher than in the C and CAD groups. Apo A-II has been shown to inhibit LCAT. High values of apo A-I and apo A-II with opposing actions within HDL was shown to be a representative characteristic of VSA. In the present study, HDL-C levels were not significantly different in the VSA group from those in the C and CAD groups, but apo A-I and A-II, as the main structural proteins of HDL had significantly higher levels in the VSA group. Thus in VSA, abnormalities of lipid metabolism including a qualitative abnormality of HDL appeared to be present. The relationship between these observations and coronary vasospasm needs to be clarified through further study.

REFERENCES

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