Contribution of Lp(a) to the Occurrence of Vascular Diseases : Correlation of Several Risk Factors Including Diabetes Mellitus

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We demonstrated that Lp(a) levels in patients with arteriosclerosis obliterans (21.4 ± 2.5 mg/dl) and in patients with ischemic heart disease (17.2 ± 0.8 mg/dl) are higher than those in controls (15.4 ± 0.7 mg/dl) or healthy controls (11.3 ± 1.1 mg/dl). Lp(a) levels in patients with these vascular diseases were especially higher when there were known atherosclerotic risk factors such as diabetes mellitus, hypercholesterolemia or hypertension, although Lp(a) levels in patients with these risk-positive group was not different from that of control. These results suggest that Lp(a) contributes to the development of atherosclerotic vascular diseases especially when known atherosclerotic risk factors are not present. We also investigated the case of thromboangiitis obliterans, which is believed to develop from non-atherosclerotic mechanisms, and found that Lp(a) levels were higher (26.5 ± 9.6 mg/dl) in such patients.

Lp(a) is recognized as an important risk factor of atherosclerotic diseases. However, the contribution of Lp(a) to the development of vascular diseases including arteriosclerosis obliterans and thromboangiitis obliterans is still not precisely known.

We measured serum Lp(a) levels in patients with arteriosclerosis obliterans and thromboangiitis obliterans, and compared these with those of patients with ischemic heart disease, controls and healthy controls. Other concomitant known risk factors of atherosclerotic diseases such as diabetes mellitus, hypercholesterolemia and hypertension were also investigated in ASO and IHD, and the contribution of Lp(a) to the development of these diseases was discussed.

Subjects

Subjects included were the patients with symptoms of intermittent claudication, ischemic pain of the lower extremities, weak pulsation of peripheral artery or ischemic skin necrosis of the toes, who were diagnosed as arteriosclerosis obliterans (ASO) or thromboangiitis obliterans (TAO), by their angiographic findings. Patients

with old myocardial infarction or angina pectoris diagnosed by coronary angiography, exercise test and Holter ECG were compared with ASO and TAO patients (Table 1). Patients receiving a periodic health check and those visiting our clinic for the treatment of diabetes mellitus, hyperlipidemia and hypertension were investigated as a control group. All control subjects were free from atherosclerotic vascular diseases such as ischemic heart disease (IHD), ASO or TAO (Tables 1, 2) (Group I).

Table 1.

Subjects

ASO, TAO :

Patients with symptoms of intermittent claudication, ischemic pain or weak pulsation of peripheral artery were angiographically diagnosed.

IHD : Old myocardial infarction, Angina Pectoris

Effort : stenosis > 75% by CAG and exercise test

Rest : ST-change by Holter ECG with symptom

Control :

Subjects who visited our clinic for :

1. Periodical medical examination
2. Diabetes, hypercholesterolemia, hypertension etc.

without vascular diseases such as ASO, TAO or IHD.

Healthy Control :

Control or subjects without DM, HC, HT.

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Table 2. Group I.

ASO	46
TAO	5
IHD	303
Control	460
(Healthy Control)	100)

Table 3. Group II*.

ASO	38
TAO	5
IHD	208
Control	176
(Healthy Control)	20)

* Male subjects over 40 y.o.

Table 4. Risk factors of vascular diseases investigated.

	n	TC (mg/dl)	s-BP (mmHg)	FPG (mg/dl)
ASO	38	205±46**	149±23**	132±48***
TAO	5	183±44	135±11	92±14
IHD	208	199±41*	139±21	117±39***
Control	176	223±69	139±24	106±27
Healthy Control	20	185±19	126±14	103± 8

Mean±SD, t-test (Welch)

* p<0.05, ** p<0.01, *** p<0.001 v.s. Healthy Controls

Male subjects over 40 years old were selected from Group I to evaluate the contribution of Lp(a) to the development of vascular diseases by evaluating coexisting risk factors such as DM, HC and HT, since gender and age affect the incidence of atherosclerotic diseases significantly (Table 3, Group II).

Risk factors such as diabetes mellitus, hypercholesterolemia and hypertension are detected as follows: Subjects with serum cholesterol greater than 220 mg/dl were classified as hypercholesterolemic (HC), and those subjects whose 75 g oral glucose tolerance test demonstrated impaired glucose tolerance or diabetes, or whose hemoglobin A1c was more than 6.5% were classified with diabetes mellitus (DM), and subjects with systolic pressure more than 160 mmHg or diastolic pressure more than 95 mmHg were classified as hypertensive (HT). Familial hypercholesterolemic cases were excluded from the study. Clinical profiles of these subjects are summarized in Table 4.

Methods

Blood sample was obtained in the morning after overnight fasting and Lp(a) levels were measured by Tint Elize Lp(a) kit, Biopool, Sweden. Mean value and standard error (Mean±SE) of serum Lp(a) level are used for graphic presentation. The data were evaluated by Mann-Whitney test.

Fig. 1. Lp(a) in IHD and ASO. **Fig. 2.** Lp(a) in Controls. **Fig. 3.** Lp(a) levels in ASO patients.

Results

In Group I, Lp(a) levels in ASO patients were higher (21.4 ± 2.5 mg/dl) than those of either healthy controls (11.3 ± 1.1 mg/dl) or controls (15.4 ± 0.7 mg/dl). Lp(a) levels of IHD patients were also higher (17.2 ± 0.8 mg/dl) than those of either healthy controls or controls (Fig. 1).

We further examined male subjects over 40 years old (Group II, Table 3). The Lp(a) levels of the controls in Group II are shown in Fig. 2, demonstrating that Lp(a) levels in controls with DM, HC or HT are slightly higher than those of risk-negative control although the difference is not statistically significant (Fig. 2).

To evaluate ASO, cases were divided into two groups on the basis of accompanying risk factors. One group had no risk factors such as DM, HC or HT, while the other group had more than one risk factor. Lp(a) levels in risk-negative ASO patients were much higher (27.0 ± 5.6

Fig. 6. Lp(a) levels in IHD and ASO patients with/without HT.

Fig. 4. Lp(a) levels in IHD and ASO patients with/without DM.

Fig. 7. Lp(a) levels in patients with TAO.

Fig. 5. Lp(a) levels in IHD and ASO patients with/without HC.

Fig. 8. Lp(a) levels in IHD patients.

mg/dl) than those of risk-negative control (12.2 ± 1.9 mg/dl), whereas Lp(a) level in risk-positive ASO patients was not higher than that in risk-positive controls (Fig. 3). When the Lp(a) level was investigated with respect to each accompanying risk factor, the tendency was the same: Lp(a) levels of DM-negative ASO patients were much higher (24.2 ± 4.1 mg/dl) than those of controls (14.1 ± 1.2 mg/dl), whereas Lp(a) levels of DM-positive ASO patients were not different from those of controls (14.8 ± 2.8 mg/dl) (Fig. 4). Lp(a) levels of HC-negative ASO patients were much higher (24.2 ± 3.9 mg/dl) than those of controls (13.8 ± 1.7 mg/dl), whereas Lp(a) levels of HC-positive ASO patients were not different from those of controls (14.8 ± 1.4 mg/dl) (Fig. 5). Lp(a) levels of HT-negative ASO patients was slightly higher (19.6 ± 4.4 mg/dl) than those of controls (15.1 ± 2.0 mg/dl) with no statistical significance, whereas Lp(a) levels of HT-negative ASO patients were higher (22.3 ± 3.8 mg/dl) than those of controls (13.9 ± 1.4 mg/dl) (Fig. 6).

We examined Lp(a) levels in patients with TAO which is thought to be developed from non-atherosclerotic risks. Lp(a) levels of TAO patients were much higher (26.5 ± 9.6 mg/dl) than those of healthy controls (11.0 ± 2.3 mg/dl) (Fig. 7). In this case, we used healthy controls for com-

parison because TAO cases had no risk factors of DM, HC nor HT.

We also examined Lp(a) levels of IHD patients with respect to accompanying risk factors. Lp(a) levels of IHD patients with DM, HC or HT were not different from those of controls, whereas Lp(a) of IHD patients without any risk factor was slightly higher (15.9 ± 1.6 mg/dl) than those of controls (12.2 ± 1.9 mg/dl) (Fig. 8).

Discussion

We demonstrated that Lp(a) level is an independent risk factor for atherosclerotic diseases such as IHD and ASO, especially when the patients are free of other risk factors. In atherosclerotic vascular diseases which accompany other risk factors such as DM, HC and HT, Lp(a) apparently contributed less to the development of the disease. We also demonstrated that Lp(a) levels of TAO patients are elevated, although the number of patients was small ($n=5$). TAO was originally thought to be an angiitis of unknown origin and its pathogenesis might be different for atherosclerosis. Further investigation is necessary before we can determine whether the Lp(a) elevation is a cause or a result of TAO.