Alterations in Serum Lp(a) Lipoprotein Concentrations in Patients with Hepatobiliary Disorders

MITSUTOSHI YAMASHIRO, MITSURU SEISHIMA and MASAKA KAWADE

SUMMARY The serum Lp(a) lipoprotein concentration in patients with hepatobiliary disorders was determined by single radial immunodiffusion, and alterations in concentration during the clinical course were observed. The Lp(a) concentration was significantly decreased in patients with liver cirrhosis or hepatocellular carcinoma (p<0.001), with fulminant hepatitis (p<0.01), and with acute hepatitis or obstructive jaundice (p<0.05). In general, the Lp(a) level did not vary so much if the liver function was stable.

From observation of the clinical course in hepatobiliary disorders, the Lp(a) concentration was found to vary inversely with changes in the GPT level, which is a parameter of liver cell damage. Its concentration roughly paralleled that of other liver function parameters. Therefore, Lp(a) is considered to be a lipoprotein whose concentration is able to change according to the degree of liver cell damage, and the data strongly suggest that Lp(a) is, at least in part, synthesized in liver cells.

Introduction

Lp(a) lipoprotein, first described by Berg1 in 1963, has been considered to be inherited as a quantitative genetic trait2,3 and later was shown to be a risk factor for atherosclerotic disease4-8. However, little is known concerning alterations in the Lp(a) concentration in various diseases.

In the present study, we determined the serum Lp(a) concentration in patients with hepatobiliary disorders and observed the alterations in its level during the clinical course of the disease.

Materials and Methods

Patients

One hundred healthy subjects, 13 patients with acute hepatitis, 23 with chronic hepatitis, 48 with liver cirrhosis, 35 with hepatocellular carcinoma, 5 with fulminant hepatitis, 12 with obstructive jaundice, and 3 with fatty liver were studied. Diagnoses were established by means of routine liver function tests, liver biopsy, or laparotomy. Blood samples were allowed to clot at room temperature for 2 hr, and
Methods

Lp(a) monospecific antisera from rabbits were prepared according to the procedure of Albers and Hazzard\(^3\), and their specificity was judged by immunoelectrophoresis. Fig. 1 shows that Lp(a)-rich human serum formed one precipitin line against anti-Lp(a) serum, which clearly differs from that against the commercially available anti-\(\beta\)-lipoprotein serum (Dakko immunoglobulins, Copenhagen).

Quantitation of Lp(a) was performed by the single radial immunodiffusion method in which 1% agarose (pH 8.6, Agarose immunodiffusion Tablets, Bio-Rad, Richmond) containing 1% Lp(a) antisera was used. A calibration curve for Lp(a) was prepared by dilution of Lp(a)-rich serum with normal saline. The secondary standards were shown to be stable for at least two months at 4°C after they were passed through 0.22 μm Millipore filters (Millipore Corp., Bedford) in the presence of 0.1% Na\(\text{NO}_3\) and EDTA-2Na.

The CV’s of the within-assay and day-to-day precision were less than 1.3% and 3.1%, respectively, at a concentration of 30 mg/dl.

Results

Serum \(\text{Lp}(a)\) concentration

Each serum was subjected to single radial immunodiffusion, and the results are summarized in Fig. 2. A log transformation was performed on each Lp(a) value because of a non-Gaussian distribution and was expressed as log mg/dl. The
Fig. 2  Lp (a) concentration in normal subjects and in patients with hepatobiliary disease. The shaded areas represent 1 SD. The median is shown by the interrupted lines. Standard deviations were calculated following log transformation.

data were tested for significance by Student's t-Test. The Lp (a) value in normal subjects was 6.3 (2.5~16.2) mg/dl; in patients with acute hepatitis, 3.7 (1.7~8.3); in chronic hepatitis, 5.0 (2.3~10.7); in liver cirrhosis, 2.3 (1.0~5.2); in hepatocellular carcinoma, 2.8 (1.1~7.2); in fulminant hepatitis, 1.8 (0~4.6); and in obstructive jaundice, 3.5 (1.5~8.1). Compared with the normal subjects, the serum Lp (a) concentration was significantly decreased in patients with liver cirrhosis and with hepatocellular carcinoma, which is generally accompanied by liver cirrhosis in Japanese (p<0.001). It was also decreased in patients with fulminant hepatitis (p<0.01) or with acute hepatitis or obstructive jaundice (p<0.05). However, it was not significantly decreased in those with chronic hepatitis (Table I).

Alteration in Lp (a) concentration

Alterations in Lp (a) concentration were observed in the case of a 21-year-old woman suffering from acute viral hepatitis. Lp (a) was not detected when the GPT level was 3190 IU/l at admission, but the Lp (a) value increased to 6 mg/dl and the GPT level dropped to 15 IU/l at

Table I  Serum Lp (a) concentration in normal subjects and in patients with hepatobiliary disorders

<table>
<thead>
<tr>
<th></th>
<th>normal subjects</th>
<th>acute hepatitis</th>
<th>chronic hepatitis</th>
<th>liver cirrhosis</th>
<th>hepatocellular carcinoma</th>
<th>fulminant hepatitis</th>
<th>obstructive jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.80±0.41</td>
<td>0.57±0.35*</td>
<td>0.70±0.33</td>
<td>0.37±0.35***</td>
<td>0.45±0.41***</td>
<td>0.25±0.41**</td>
<td>0.55±0.36*</td>
</tr>
</tbody>
</table>

Data are presented after log transformation ±SD(mg/dl).

*p<0.05; **p<0.01; ***p<0.001.
Alterations in Serum Lp(a) Lipoprotein Concentrations in Patients with Hepatobiliary Disorders

Acute hepatitis

Fig. 3 Follow up of Lp(a) concentration, GPT, Thrombo test, Normo test, and choline esterase in the course of a patient with acute hepatitis.

Chronic hepatitis (HBV carrier)

Fig. 4 Follow up of Lp(a) concentration, GPT, and total bilirubin in the course of a patient with chronic hepatitis given prednisolone therapy.
discharge. Thrombo test and choline esterase values were also increased (Fig. 3). And we observed similar alterations in the Lp(a) concentration in almost all other cases of acute hepatitis.

The HBV carrier with chronic hepatitis is sometimes given prednisolone therapy for the purpose of the seroconversion from HBe Ag to HBsAb. In the case of a 19-year-old man who was seropositive for HBsAg, the Lp(a) value was increased to 30 mg/dl from 10 mg/dl and the GPT level was decreased by administration of prednisolone. However, the GPT level increased to 819 IU/l by a rebound phenomenon and the Lp(a) value decreased to 3 mg/dl after the therapy (Fig. 4). However, the Lp(a) value did not vary so much in other patients with chronic hepatitis in which liver function was stable.

On the other hand, the Lp(a) value remained low throughout the clinical course in patients with liver cirrhosis or with hepatocellular carcinoma.

**Discussion**

Intensive investigations have shown that the lipid composition of Lp(a) is very similar to that of low density lipoprotein (LDL) and, its apolipoproteins consist of apolipoprotein B, the major component of LDL, and Lp(a)-specific antigen. In addition, it has been shown that Lp(a) is not converted to other lipoproteins nor is it taken up by the LDL receptor pathway as is LDL. However, no information is available regarding the biological function of Lp(a).

In the present study, we have shown that the Lp(a) value was significantly decreased in patients with various hepatobiliary disorders, particularly in those with liver cirrhosis or with hepatocellular carcinoma, compared with the value found for normal subjects. In all of the cases of acute hepatitis, Lp(a) values varied inversely with the change in the GPT level during the clinical course.

In general, big alterations in the Lp(a) concentration could not be observed in patients with chronic hepatitis if they were in a stable condition. The case of chronic hepatitis whose data is shown in Fig. 4 is a particular one in which prednisolone was administered intentionally. An alteration in the Lp(a) concentration was observed in this case, though it was obscure whether it was due to a direct effect of prednisolone. However, we could not find a constant relationship between Lp(a) concentration and the dose of prednisolone in patients with non-hepatobiliary disorders who were given prednisolone therapy. Therefore, it appears that the alteration in Lp(a) concentration is influenced by the degree of liver cell damage but not by the direct action of prednisolone. On the other hand, the Lp(a) concentration remained at a low level throughout the clinical course in patients with liver cirrhosis or with hepatocellular carcinoma.

From these results, we conclude that generally in patients with hepatobiliary disorder, though the Lp(a) value does not vary so much if the liver function is stable, it may fluctuate according to changes in liver function. Therefore, it is strongly suggested that Lp(a) is at least partly synthesized in liver cells. Studies are now in progress in our laboratory for the direct demonstration of Lp(a) synthesis in liver cells by a histochemical method.
Alterations in Serum Lp(a) Lipoprotein Concentrations in Patients with Hepatobiliary Disorders

Acknowledgement

This study was supported partially by a grant from the Clinical Pathology Research Foundation of Japan.

References