Serum lipoprotein (a) levels in liver diseases caused by hepatitis

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Lipoprotein (a) [LP(a)] is a genetic variant of low density lipoprotein (LDL) and is mainly synthesized in liver. We conducted a study to evaluate the association of serum [Lp(a)] level with hepatitis viral infections. A total of 130 patients including 50 patients with acute viral hepatitis (AVH), 30 with chronic active hepatitis (CAH), 30 with cirrhosis of liver and 20 patients with fulminant hepatic failure (FHF) were analysed for different hepatitis viral markers and Lp(a) level in their serum samples. For comparison, 50 healthy persons were also tested for Lp(a) level. Serum Lp(a) level in patients in all the disease groups was significantly reduced compared to that observed in controls. Lp(a) level could not be detected in 40 per cent cases with AVH, 46.6 per cent with CAH, 70 per cent with cirrhosis and 80 per cent of FHF patients. On correlating Lp(a) level to viral etiology in these patients, it was found that the extent of diminution in Lp(a) level did not follow any trend with some particular viral infection and was recorded nearly same in all the infections. The findings of this study suggested that serum Lp(a) level was significantly (P<0.001) reduced in patients with liver diseases irrespective of the viral etiology.

Key words HBV - HCV - hepatitis - HEV

Lipoprotein (a) [Lp(a)] is a circulating particle closely related to low density lipoprotein (LDL). It is a genetic variant of LDL and consists of covalent association of the unique and enigmatic apolipoprotein (a) to apolipoprotein B-100 by a single disulphide bridge.

The metabolism of Lp(a), from synthesis to catabolism is not clear. More than 90 per cent of Lp(a) level is under genetic regulation and greater part is accounted for by size polymorphism in the sequence of apo(a) gene. Besides, metabolic abnormalities, such as the acute phase response, hormone disorders, diabetes and liver and renal failure have strong influence on Lp(a) levels in plasma, suggesting that factors other than genetic may also play a central role in the intricate metabolism of the lipoprotein.

It has been reported that raised Lp (a) concentrations have relation with genesis, progression and complications of both atherosclerosis and thrombosis. These findings caused an interest among researchers to correlate serum/plasma Lp(a) level with clinical informations and use this parameter to predict the risk of cardiovascular or thrombotic diseases in patients belonging to various other disease groups.
The present study was planned to quantitate Lp(a) level in patients with various forms of liver diseases caused by hepatitis viral infections to establish the possible relationship between different viral infections and circulating Lp(a) level.

A total of 130 adults patients of both sexes were included in the present study. These included 50 patients (age range: 21-48 yr) with acute viral hepatitis (AVH); 30 (age range: 19-48 yr) with chronic active hepatitis (CAH), 30 (age range: 34-57 yr) with cirrhosis of the liver, and 20 patients (age range: 28-46 yr) with fulminant hepatic failure (FHF). These patients attended either outpatient department or were admitted to the liver unit of All India Institute of Medical Sciences (AIIMS), New Delhi, during March 1999 to February 2002. They were evaluated clinically and biochemically and their sera were tested for hepatitis viral markers. The diagnosis of different types of liver diseases was based on accepted clinical, biochemical and histological criteria. None of the patients had a past history of alcohol intake or using any drug. Fifty age and sex matched healthy individuals were included as controls.

From each patient, 6-10 ml of venous blood was drawn and aliquoted in plain tubes without anticoagulant. Serum was separated after centrifugation and then stored at -70°C until further analysed for hepatitis viral markers and Lp(a). Sera were investigated for hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis A virus (IgM anti-HAV), hepatitis B core antigen (IgM anti-HBc) (kits from Abbot Laboratories, USA), hepatitis D virus (IgM anti-HDV) (kit from Wellcome, UK) and hepatitis E virus (IgM anti-HEV) (ELISA kit from Genlabs & Diagnostics, Singapore). Similarly, all these sera were also tested for total antibodies against hepatitis C virus (anti-HCV) using highly sensitive third generation ELISA kit from Ortho diagnostics, UK.

Lp(a) level in serum samples was estimated by a specific and sensitive immunoturbidimetric assay where agglutination occurs due to an antigen-antibody reaction between Lp(a) in a sample and anti-Lp(a) antibody adsorbed to latex particles. This agglutination is detected as an absorbance change at 700 nm proportional to the concentration of Lp(a) in the sample. Lp(a) estimation was done on autoanalyser Hitachi-917, Japan using test kits from Randox laboratories, UK. The standards and control samples to calibrate equipment for serum Lp(a) level were also obtained from Randox Laboratories, UK.

The diagnosis of HAV infection was confirmed by the presence of IgM anti-HAV in serum HBV by the presence of IgM anti-HBc in sera of AVH and FHF patients and by the persistent HBsAg antigenaemia and/or presence of IgG anti-HBc in sera of CAH and cirrhosis cases. Presence of IgM anti-HCV and IgM anti-HDV in sera samples was used for the diagnosis of HCV and recent HDV infections, respectively. Active or recent HEV infection was diagnosed by the presence of IgM anti-HEV in serum. Sera positive for HBsAg but negative for all other viral markers were labelled as HBV-carriers. Absence of all the markers including HBsAg labelled the patients with hepatitis non-ABCDE infection on exclusion criteria.

HAV and HDV infections were absent in all the patients. AVH patients had hepatitis B infection in 10 cases, hepatitis C in 2 and hepatitis E in 16 patients, respectively. Three patients had mixed BCE infection. Four patients had no marker and were labelled as hepatitis non-BCE cases; 15 patients were positive for HBsAg only and labelled as HBV-carriers. CAH patients had hepatitis B, C and mixed BC infection in 11, 7 and 7 patients, respectively. Five patients had no marker and labelled as hepatitis non-BC cases. In cirrhosis group, hepatitis B,C, mixed BC and non-BC were detected in 8, 6, 1 and 15 cases, respectively. In FHF group, hepatitis B, C, E and mixed BCE infection was recorded in 4, 7, 7 and 1 cases, respectively. One patient was detected with non-BCE infection and none found to be the HBV-carrier.
Lp(a) level in all the patients with different liver diseases, irrespective of viral etiology, was found to be significantly diminished ($P < 0.001$) as compared to controls. Interestingly, Lp(a) level was not detected in 20 of 50 (40%) patients with A VH, 14 of 30 (46.6%) patients with CAH, 21 of 30 (70%) with hepatic cirrhosis, and 16 of 20 (80%) patients with FHF. Five patients with A VH, who were followed up for six months, showed an increasing level of serum Lp(a) with recovery of the disease. The mean value of Lp(a) observed in acute phase ($9.2 \pm 3.6$ mg/dl) of these five patients reached to $22.4 \pm 4.0$ mg/dl after six months of recovery.

Lp(a) was first demonstrated by Berg in 1963$^{14}$ as a circulating particle which consists of apolipoprotein B-100 linked to apolipoprotein (a) by a disulphide bridge. Liver is the major source of circulating Lp(a)$^{15,16}$. This finding was also confirmed by the observation that after liver transplantation, the recipients acquired donors’ apo(a) phenotype$^{17}$. Subsequent studies reported that it is apo(a) and not the total Lp(a) particle, which is secreted by the hepatocyte$^{18}$, and this apo(a) is extracellularly linked to apo B-100 on liver cell surface$^{19}$.

Some studies have described a possible relation between Lp(a) and liver diseases. Geiss et al$^{20}$ demonstrated acute viral hepatitis with diminished Lp(a) serum concentration. Valimaki et al$^{21}$ reported low Lp(a) in chronic liver diseases of different etiology. Our study showed that both acute and chronic liver diseases including cirrhosis of liver were associated with diminished serum Lp(a) concentrations. Lp(a) concentrations tended to be reduced in high proportions in patients with more severe forms of liver diseases like FHF and cirrhosis of liver as compared to acute and chronic liver failure (Table). Absence of detectable Lp(a) level in some patients is in agreement with the findings of Feely et al$^8$ who could not detect Lp(a) level in patients with hepatic cirrhosis. Since liver is the organ synthesising Lp(a)$^{16,17}$, reduced Lp(a) level during liver diseases was supposed to result from its diminished synthesis by the damaged liver. This view is also supported by other studies$^{8,22,23}$. Our data indicate that there is an apparent decline in Lp(a) level in all types of hepatitis viral infections. Though, reduction in Lp(a) level does not appear to follow any trend in relation to the causative hepatitis virus, it seems that reduction in Lp(a) level is not dependent on the nature of causative virus.

In conclusion, serum Lp(a) level in patients with liver diseases induced by hepatitis viral infections was significantly reduced compared to healthy controls. Reduction in Lp(a) level appears to be independent of causative hepatitis viral infection.

### Table. Serum Lp(a) level in different liver diseases

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Lp(a) level (mg/dl)</th>
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<tbody>
<tr>
<td>Acute viral hepatitis (AVH)</td>
<td>7.4 ± 15.3*</td>
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<tr>
<td>Chronic active hepatitis (CAH)</td>
<td>10.3 ± 18.2*</td>
</tr>
<tr>
<td>Cirrhosis of liver</td>
<td>6.7 ± 12.9*</td>
</tr>
<tr>
<td>Fulminant hepatic failure (FHF)</td>
<td>10.2 ± 14.9*</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>15.4 ± 13.1</td>
</tr>
</tbody>
</table>

* P<0.001 compared to control

### References


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