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Serum Lipoprotein(a) Level is Decreased in Patients with Liver Diseases†

Jin Q Kim, Young Joon Hong, Jung Han Song, Sung Sup Park, Hyo Suk Lee[1], Chung Yong Kim[1] and Sang In Kim

Department of Clinical Pathology and Department of Internal Medicine[1], Seoul National University College of Medicine, Seoul 110-744, Korea

=Abstract=**Although the synthesis and metabolism of lipoprotein(a) [Lp(a)] are not clearly understood, the liver is considered to be the main site of Lp(a) synthesis. We measured the serum concentration of Lp(a) and of other lipid parameters in 153 patients with various liver diseases(10 chronic or toxic hepatitis, 76 liver cirrhosis and 67 primary liver cancer). The serum Lp(a) was significantly decreased or even undetectable in liver diseases compared with the normal control group and the decrease of Lp(a) was more remarkable than the other lipid parameters. But there were no significant differences between the 3 groups of liver diseases. Thus we suggest the possibility of Lp(a) measurement as a novel, sensitive parameter assessing dysfunction of the liver, regardless of dyslipidemic condition.**

Key Words: *Liporotein(a), Liver diseases*

INTRODUCTION

Lipoprotein(a) [Lp(a)] is an LDL-like particle with a large glycoprotein called apo(a) attached to its apo B moiety through disulfide bond (Eaton *et al.* 1987;Mclean *et al.* 1987). Many case-control studies have shown that plasma Lp(a) levels are associated with premature coronary heart disease (Rhoads *et al.* 1986; Utermann 1989; Kostner *et al.* 1981; Kim *et al.* 1992) and thrombotic diseases (Scott 1989; Miles *et al.* 1989) because of its atherogenic as well as thrombogenic properties.

The main site of the synthesis of Lp(a) is the liver (Tomlinson *et al.* 1989; Rainwater *et al.* 1989; Kraft *et al.* 1989). Thus the rate of its synthesis is believed to be regulated not only by genetic composition (Utermann *et al.* 1987; Kim 1992) but also by the functioning liver. So we measured serum cholesterol, triglyceride and HDL-cholesterol in various groups of liver diseases to evaluate changes caused by liver dysfunction.

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서울대학교 의과대학 임상병리과학교실 : 김진규, 홍영준, 송정한, 박성섭, 김상인
서울대학교 의과대학 내과학교실 : 이효석, 김정룡

MATERIALS AND METHODS

Patients and control groups. Patients included in this study were 100 males and 53 females, aged between 35 and 65 years (mean age 50). They were clinically diagnosed with various liver diseases, consisting of 10 toxic or chronic active hepatitis, 76 liver cirrhosis(LC) and 67 primary liver cancer(PLCA). Values for control individuals were taken from previously studied data, Kim JQ *et al.*(1991) for serum Lp (a) and Choi KH *et al.*(1990) for other lipid parameters. Blood samples of both control groups were obtained from apparently healthy subjects who had no significant physical and laboratory abnormalities on routine check.

Determination of Lp(a). Serum Lp(a) concentration was measured by an enzyme-linked immunosorbent assay using a commercially available kit (Immuno AG, Vienna, Austria). The detection limit was 1.0 mg/dL.

Determination of other lipid parameters. Serum total cholesterol, triglyceride and HDL-cholesterol were assayed in a standard clinical laboratory. Blood samples were drawn after a 14 hour fast. Sera were separated within 2 hours by low speed centrifugation and stored at -70° C until assay. Total cholesterol and triglyceride were measured by a cholesterol oxidase enzymatic method and a glycerol oxidase enzymatic method, respectively. Both assays were performed with a Hitachi 736-40 chemistry analyzer(Hitachi, Ltd. Tokyo, Japan). HDL-cholesterol was measured by dextran sulfate-$MgCl_2$ precipitation method.

Statistical Analysis. Data analysis was performed with the Statistical Analysis System (SAS). The difference between control group and all patients in serum Lp(a) level was examined by Student *t*-test and differences between liver disease groups were examined by the 1 way ANOVA test respectively.

RESULTS

Frequency distributions of serum Lp(a) concentrations of controls and patients with liver diseases are shown in Fig. 1. Mean serum concentration of Lp(a) and other lipid parameters in patients with liver diseases are listed in Table 1. Mean serum Lp(a) concentration of patients was 4.5 mg/dL, which is significantly lower than that of the control group, 14.9 mg/dL($p < 0.001$ by Student *t*-test). Mean Lp(a) concentration in the hepatitis group was 2.2 mg/dL, in the liver cirrhosis group, 4.7 mg/dL and in the primary liver cancer group, 4.6 mg/dL. The differences in Lp(a) levels between the patients with liver diseases and control groups were more remarkable than those of conventional lipid parameters such as cholesterol, triglyceride and HDL-cholesterol (Fig. 2). But the differences in Lp(a) levels between the 3 groups with liver diseases are statistically insignificant (p=.6188by 1 way ANOVA test).

DISCUSSION

It was the major goal of this study to investigate the influence of liver damage on the serum concentration of Lp(a). It is well-known that the serum concentration of apolipoprotein (a), the unique protein of Lp(a), is genetically controlled to a major degree and not modified by age, sex, and changes in diet, life style, or therapy with most lipid-lowering drugs except nicotinic acid (Fless *et al.* 1984; Carlson *et al.* 1989; Kim *et al.* 1991). Our result also revealed that the serum Lp(a) concentrations were not affected by age, sex and life style both in control and liver disease groups. The presence of apo (a) mRNA in human, baboon, and rhesus monkey liver and in the Hep G2 cell line is proven (Rainwater *et al.* 1988). In individuals undergoing therapeutic liver transplantation, it was found that a complete conversion of the apo (a) phenotype of the recipient to that of the donor

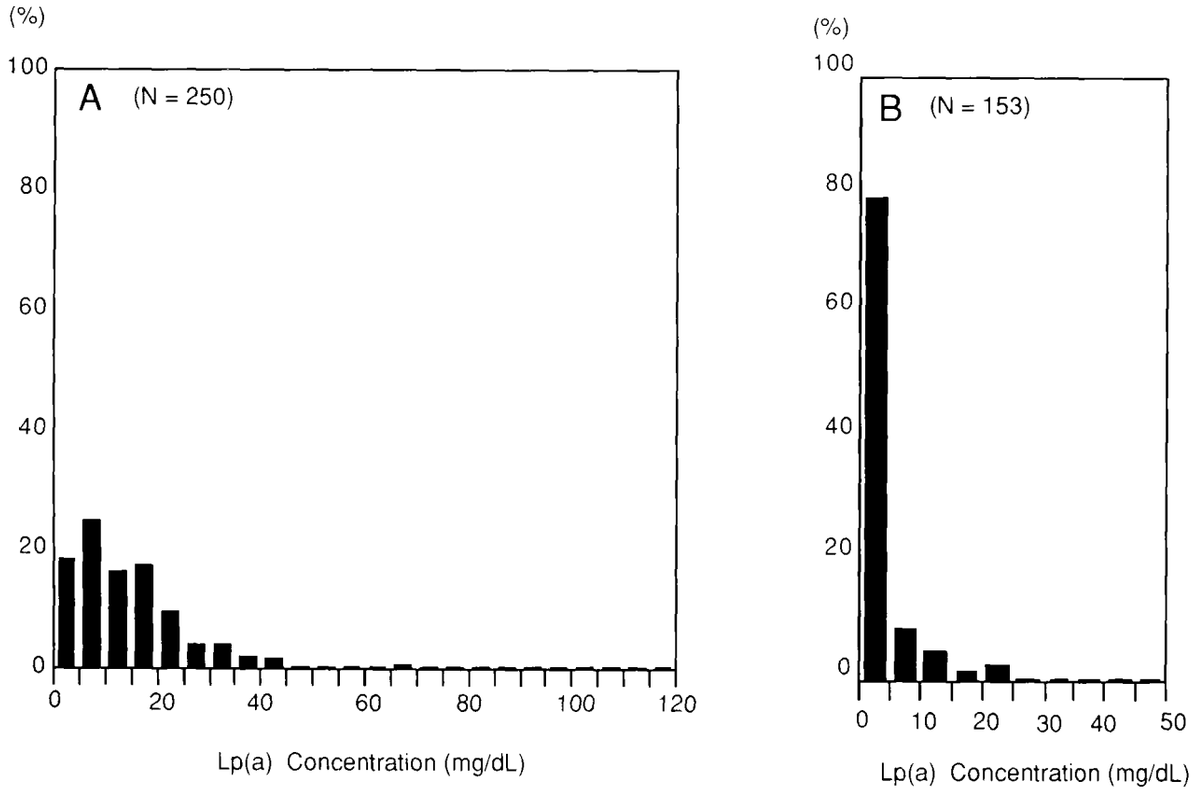

Fig. 1. Frequency distribution of Lp(a) concentration in normal Korean population(A) and in patients with liver diseases(B).

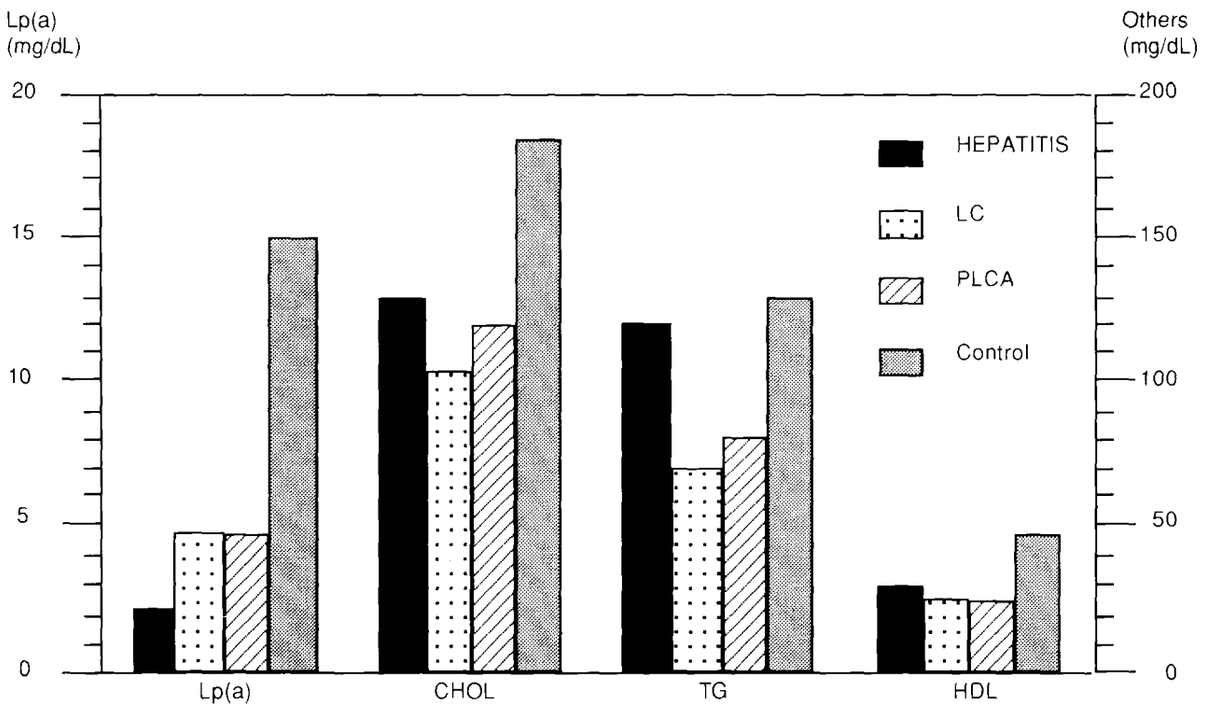

Fig. 2. Lp(a) and other lipid parameters in various liver diseases.

Table 1. Mean concentrations of serum Lp(a) and other lipid parameters in the control group and in patients with liver diseases (Unit: mg/dL)

	Control	Hepatitis (n = 10)	LC (n = 76)	PLCA (n = 67)	All Patients (n = 153)
Lp(a)* (mean ± 2SD)	14.9 ± 12.9[a]	2.2 ± 1.4	4.7 ± 8.5	4.6 ± 7.1	4.5 ± 7.6
Total cholesterol	185.0[b]	129.7	103.5	118.8	117.3
Triglyceride	129.6[b]	120.4	69.8	80.6	90.3
HDL-cholesterol	45.8[b]	29.1	25.3	24.2	26.2

[a] Values taken from 250 subjects (Kim JQ *et al*, 1991)

[b] Values taken from 3109 subjects (Choi KH *et al*, 1990)

* Lp(a) between the control group and all patients: $p < 0.001$ by Stuent *t*-test
Lp(a) between the liver disease groups: $p = 0.6188$ by ANOVA test

occurs after liver transplantation (Kraft *et al.* 1989). Thus the major site of synthesis of serum apo(a) appears to be the liver. Although apo(a) production in the testes and in the brain in rhesus monkeys has been reported (Tomlinson *et al.* 1989), it is unlikely to indicate that these tissues are a site of active secretion. Marth *et al.* (1982) reported that Lp(a) levels in heavy chronic ethanol drinkers are decreased due to modified liver function by ethanol.

In our results, the serum concentration of Lp (a) is markedly decreased in patients with liver diseases. Although the skewed distribution of Lp (a) levels in the normal population is considered, the concentration of Lp(a) in liver diseases was significantly lower than that of the control group. Lp(a) level was less than 5 mg/dL in 80% of patients and about two thirds of all the patients showed an Lp(a) level which was near the detection limit of 1 mg/dL or even undetectable. These results are probably due to decreased synthesis of Lp(a) in the liver. But a follow-up study of Lp(a) levels in the patient group should be performed. It seems that there is no quantitative correlation between decrease of serum Lp(a) level and disease activity since the differences between each liver disease group were not significant. From in vivo turnover studies of Lp(a) in humans, it has been concluded that differences in plasma Lp(a) concentrations among individuals are a result of differences in synthesis rather than by differences in catabolism. The differences in Lp (a) levels between patients and control groups are more remarkable than those of other conventional lipid parameters and some patients in our study showed decreased Lp(a) level without any significant alterations in serum protein and transaminase level.

In conclusion, the measurement of serum Lp (a) can be a sensitive method for assessing liver dysfunction.

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