A Study of the Clinical Significance of Lipoprotein (a) in Nephrotic Syndrome

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Lipoprotein (Lp)(a) concentrations were measured in eight patients with nephrotic syndrome in the age range of 8 to 69 yrs. Mean ($\pm$ SE) levels of serum Lp(a) were elevated in the nephrotic patients compared to controls (76.5 ± 19.7 vs 18.6 ± 0.9 mg/dl, $p < 0.001$). After treatment with prednisolone, Lp(a) concentrations were decreased from 85.2 ± 21.6 to 42.2 ± 14.0 mg/dl. During the treatment, serum total cholesterol showed a negative correlation with serum albumin concentration. However, no correlation was noted between Lp(a) and serum albumin concentration. There were no significant correlations between Lp(a) and other lipoprotein lipid and apolipoprotein levels. It was concluded that hyperLp(a) aemia may be an independent risk factor in the development of premature atherosclerosis in patients with nephrotic syndrome.

Key words: Atherosclerosis, HyperLp(a)aemia

Lipoprotein(a)[Lp(a)] level is known to be elevated in patients with ischemic heart disease (IHD). Although the pathogenesis of arteriosclerotic changes in patients with nephrotic syndrome remains to be elucidated, hyperlipoproteinemia associated with nephrotic syndrome and corticosteroid therapy may, in part, play an important role in the development of premature atherosclerosis. The authors recently reported a case of nephrotic syndrome presenting hyperLp(a)aemia accompanied by myocardial infarction and cerebral infarction in a case of systemic lupus erythematosus (1). In the present study, serum Lp(a) concentrations were determined in order to investigate any abnormalities of lipoprotein metabolism in patients with nephrotic syndrome.

SUBJECTS AND METHODS

Subjects were twelve previously untreated patients with nephrotic syndrome (8 males and 4 females,

average age 31 ± 13 yrs), who have been under treatment and hospitalized in our hospital. Healthy normal subjects were used for comparison. Renal biopsy specimens were determined by light microscopy and a fluorescent antibody method (Table 1). Fasting blood samples were drawn for serum lipoprotein analysis. According to the method of Havel et al (2), lipoprotein was separated into very low density lipoproteins (VLDL), intermediate (IDL), low (LDL) and high (HDL) density lipoproteins by preparative ultracentrifugation at densities of 1.006, 1.019, 1.063 g/ml using a Hitachi model 55p-7 Ultracentrifuge (Hitachi Koki Co., Tokyo, Japan). Cholesterol (TC) and triglyceride (TG) concentrations in serum and each fraction of lipoprotein were determined by an enzymatic method using a commercially available kit (Kyowa Medex Co., Tokyo, Japan). Lipoprotein electrophoresis was performed by means of 1% agarose film using tricine-lithium buffer (pH 8.6) and disc

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Table 1. Clinical characteristics of 12 untreated patients with nephrotic syndrome.

No.	Case	Age (yr)	Sex (F/M)	Ht (cm)	Wt (kg)	Percent of ideal body weight	Choles- terol (mg/dl)	Trigly- ceride (mg/dl)	Lp(a) (mg/dl)	ApoB (mg/dl)	Total protein (g/dl)	Albumin (g/dl)	BUN (mg/dl)	Creati- nine (mg/dl)	Renal biopsy*
1)		42	M	164	70	120	644	262	221		5.3	2.0	11	0.9	—
2)		27	M	167	61	107	239	105	13		4.6	1.7	12	1.2	Minimal change
3)		22	M	175	66	102	454	201	67		4.7	2.1	23	1.1	Minimal change
4)		28	F	142	47	112	448		63		4.1	1.6	23	1.1	Lupus nephritis
5)		21	M	163	60	103	309	179	197	296	6.6		11	0.9	Lupus nephritis
6)		23	M	180	66	94	357	179	28	127	4.7	1.8	43	1.0	Minimal change
7)		8	M	128	25	89	634	334	29		4.6	1.4	18	0.8	—
8)		69	F	140	40	100	337	259	18	157	5.5	2.6	14	1.3	—
9)		50	M	150	53	94	652	266	64	236	3.3	1.8	123	2.7	Minimal change
10)		50	F	160	54	98	239	180	140	158	7.6	3.0	17	0.9	Lupus nephritis
11)		14	F	145	39	87	293	147	59	111			27	1.4	Focal GN
12)		17	M	171	44	72	287	301	19	125	5.3	3.4	40	1.8	Lupus nephritis
Mean		31		157	52	98	408	219	77	172	5.1	2.1	30	1.3	
SD		17		15	13	12	151	67	68	63	1.1	0.6	30	0.5	

* Focal GN, focal glomerulonephritis

electrophoresis was performed using 3.6% polyacrylamide gels as described by Narayan et al (3). The concentrations of serum apolipoprotein were measured by single radial immunodiffusion using plates obtained from Daiichi Kagaku Co., Tokyo, Japan (4). Quantitation of Lp(a) was determined using a single radial immunodiffusion method in which 1% agarose (PH 8.6, Agarose immunodiffusion tablets, Bio-rad, Richmond, Virginia) containing 1% Lp(a) antiserum was used (5). The courses of 8 cases could be followed up with the collection of blood samples being performed after an improvement of serum protein level and the disappearance of urine protein or its diminution to less than 0.5 g/day. Informed consent was obtained from all individuals prior to beginning the study.

RESULTS

Table 2 shows TC and TG values of lipoprotein for all healthy normal subjects and untreated patients with nephrotic syndrome, before and after treatment. TC and TG in whole serum, VLDL, IDL, LDL and HDL before treatment showed significantly higher values than the controls, as was the same as TC in whole serum, LDL and HDL and as TG in whole serum, IDL, LDL and HDL after treatment. As far as the nephrotic syndrome as a whole was concerned, Lp(a) showed significantly higher values, 76.5 ± 19.7 mg/dl compared with 18.6 ± 0.9 mg/dl, for healthy normal subjects (mean $\pm$ SE) (Fig. 1). In the comparison of between before and after treatment with prednisolone, TC

Table 2. Serum lipid, lipoprotein, apoprotein B and Lp(a) levels in patients with nephrotic syndrome before and after treatment with prednisolone.

	n	Cholesterol (mg/dl)					Triglyceride (mg/dl)					Lp(a)	Apo B
		Total	VLDL	IDL	LDL	HDL	Total	VLDL	IDL	LDL	HDL	(mg/dl)	
Before treatment	8	459 $\pm$ 159 [#]	30 $\pm$ 3 [#]	22 $\pm$ 18 [#]	267 $\pm$ 120 [#]	90 $\pm$ 37 [#]	218 $\pm$ 67 [#]	82 $\pm$ 54 [*]	25 $\pm$ 14 [#]	68 $\pm$ 37 [*]	25 $\pm$ 11 [#]	85 $\pm$ 26	172 $\pm$ 63
After treatment	8	243 $\pm$ 43 [#]	17 $\pm$ 8	11 $\pm$ 4	138 $\pm$ 28 [#]	84 $\pm$ 22 [#]	130 $\pm$ 82 [#]	60 $\pm$ 69	19 $\pm$ 15 [#]	30 $\pm$ 14 [#]	21 $\pm$ 4 [#]	42 $\pm$ 14	115 $\pm$ 18
Normal subjects	20	183 $\pm$ 28	14 $\pm$ 7	6 $\pm$ 3	98 $\pm$ 23	48 $\pm$ 73	89 $\pm$ 32	42 $\pm$ 24	6 $\pm$ 3	17 $\pm$ 6	15 $\pm$ 3	18 $\pm$ 10	96 $\pm$ 5

All values are mean $\pm$ SD. *p<0.02, # p<0.001 compared with normal subjects.

Fig. 1. Mean ($\pm$ SE) levels of Lp(a) in normal controls and nephrotic patients (NS).

Fig. 2. Serum lipid and Lp(a) levels before and after treatment in nephrotic patients.

was significantly decreased. Apo B also showed a decreasing tendency. HDL-C remained unchanged. Lp(a) concentrations were decreased from 85.2 ± 26.1 to 42.2 ± 14.0 mg/dl but this decrease was not statistically significant (Fig. 2). Figure 3 shows the

Fig. 3. Relationship between serum total protein (TP) and serum lipid and Lp(a) concentrations in patients with nephrotic syndrome.

relationship of serum lipid levels before and after treatment; TC and serum protein showed a significant negative correlation, but neither correlation was noted among TG, HDL-C, apo B and Lp(a). No significant correlation was noted with BUN, creatinine, dose of steroid, morbid period, age, proteinuria, blood pressure or body wt.

DISCUSSION

Lp(a) lipoprotein was first described in 1963 as a genetic variant of beta lipoprotein which is inherited as an autosomal dominant trait (6). Many studies have been conducted on the relationship of Lp(a) with ischemic heart disease from 1970 (7-13). Through protein sequencing and cDNA cloning, McLean et al reported that apo(a) is very similar to human plasminogen, the precursor of the proteolytic enzyme plasmin which dissolves fibrin clots (14). Recent studies have suggested that the competition of Lp(a) and plasminogen for cellular

Table 3. Correlation coefficients between Lp(a) and serum lipoprotein and apo B levels in patients with nephrotic syndrome.

Variables*	r	p value [#]
TC	0.33	NS
VLDL-C	0.09	NS
IDL-C	0.32	NS
LDL-C	0.28	NS
HDL-C	0.21	NS
LDL-C/HDL-C	0.18	NS
TG	-0.03	NS
VLDL-TG	-0.24	NS
IDL-TG	0.14	NS
LDL-TG	0.37	NS
HDL-TG	0.11	NS
Apo B	0.36	NS

* TC, total cholesterol; TG, triglyceride; VLDL, very-low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[#] NS, not significant.

binding sites might contribute to the thrombotic and atherosclerotic risks associated with elevated Lp(a) levels (15). According to Kawade (16), 70% of healthy normal subjects show Lp(a) values of less than 10 mg/dl with no sex difference or age difference, and subjects with a high level of Lp(a) had a higher prevalence of IHD than those with a low level.

The lowered Lp(a) concentrations after treatment in untreated patients with nephrotic syndrome in the present study suggests elevated Lp(a) synthesis of the liver. However, in view of the absence of correlation of Lp(a) with serum protein and other fractions of lipoprotein, the kinetics of Lp(a) in nephrotic syndrome necessitates further examination. According to Kohtoku et al, the disappearance of the broad mid-band pattern after their remission, which disc electrophoresis revealed at a high frequency in patients with nephrotic syndrome, suggests the involvement, in its appearance, of lowering of serum albumin and the leakage of protein and other substances into the urine (17). Here, Lp(a) was noted as a single sharp band between VLDL and LDL by disc electrophoresis. In addition, a part of the above band had a high possibility of being Lp(a).

In summary, hyperLp(a)emia, which occurs at

a high incidence in untreated patients with nephrotic syndrome was suggested to be an independent risk factor in arteriosclerotic heart disease in patients with nephrotic syndrome.

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