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Hyperlipoprotein(a)aemia in nephrotic syndrome

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Abstract. The nephrotic syndrome is frequently associated with hyperlipidaemia and hyperfibrinogenaemia, leading to an increased coronary and thrombotic risk, which may be enhanced by high lipoprotein (a) [Lp(a)] concentrations. We followed the quantitative and qualitative pattern of plasma lipoproteins over 18 months in a patient with nephrotic syndrome suffering from premature coronary artery disease and with elevated level of Lp(a) (470 mg dL^{-1}). Analysis of kinetic parameters after heparin-induced extracorporeal plasma apheresis revealed a reduced fractional catabolic rate for both low-density lipoprotein (LDL) and Lp(a). After improvement of the nephrotic syndrome, Lp(a) decreased to 169 mg dL^{-1} and LDL concentrations were normalized. The decrease of Lp(a) was associated with an increase in plasma albumin concentrations. Analysis of apo(a) isoforms in the patient showed the presence of isoform S2 (alleles 10 and 19). Consequently, the authors' present strategy is to normalize the elevated Lp(a) and fibrinogen levels. For this purpose heparin-mediated extracorporeal LDL precipitation (HELP) apheresis is a promising regimen, helping to reduce the thrombotic risk and prevent coronary and graft atherosclerosis as well as the progression of glomerulosclerosis in our patient.

Keywords: Hypercholesterolaemia, hyperfibrinogenaemia, LDL-apheresis, lipoprotein (a), Lp(a) kinetic, nephrotic syndrome.

Introduction

Plasma concentrations of cholesterol and triglycerides are frequently elevated in patients with nephrotic syndrome. This type of hyperlipoproteinaemia is mainly caused by an increase in atherogenic lipoproteins containing apolipoprotein B-100 as major apolipoprotein [1]. Recent observations have indicated that some patients with nephrotic syndrome show an increase in lipoprotein (a) [(Lp(a)], a lipoprotein particle associated with elevated coronary heart disease (CHD) risk [2–4].

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The elucidation of the structure of apo(a), the characteristic apoprotein of the lipoprotein Lp(a), has revealed a high homology to kringle 4 domains of human plasminogen [5]. This similarity provides a tentative link between the plasma lipoproteins and the clotting system [6]. Lp(a) plasma levels are under tight genetic control, independent of low-density lipoprotein (LDL) plasma concentrations and refractory to dietary or drug treatment [7]. Utermann *et al.* [8] have shown an inverse correlation between the size of apo(a) isoforms, that is the number of repeated kringle 4 domains, and the plasma Lp(a) concentration.

We measured lipoprotein parameters in hospitalized patients with longstanding nephrotic syndrome. One of these patients was also suffering from severe coronary artery disease, and had an extremely elevated level of Lp(a). Plasma lipoproteins were followed in detail in this patient in order to elucidate the underlying cause of the elevated Lp(a) levels.

The patient was treated with plasma apheresis using the heparin-mediated extracorporeal LDL precipitation (HELP) procedure, which effectively eliminates plasma LDL, Lp(a) and fibrinogen [9,10]. We followed the kinetics of post-apheresis return of LDL, Lp(a) and fibrinogen to calculate their synthetic and fractional catabolic rates [11].

Methods

Clinical follow-up of the patient

In December 1979 at 42 years of age, the patient (D.K.) underwent a myocardial infarction. At this time two coronary risk factors were noted: smoking of 20 cigarettes per day for about 10 years and a mild hypercholesterolaemia (total cholesterol 250 mg dL^{-1}, 6·5 mmol L^{-1}). The patient stopped smoking after the heart attack. During the next 10 years, plasma cholesterol concentrations ranged between 200 and 250 mg dL^{-1} (5·2–6·5 mmol L^{-1}).

In November 1989, the patient was diagnosed as having perimyocarditis accompanied by a small pericardial effusion. A few months later, he developed

tibial oedema accompanied by accelerated erythrocyte sedimentation rate, decreased total serum protein concentration (51 g L^{-1}) and marked proteinuria (12·7 g day^{-1}). Kidney biopsy showed diffuse membranous glomerulonephritis. Plasma cholesterol concentrations were above 400 mg dL^{-1} (10·4 mmol L^{-1}), and triglyceride concentrations ranged between 136 (1·6 mmol L^{-1}) and 367 mg dl (4·2 mmol L^{-1}). Standard treatment with chlorambucil and prednisolone, which was continued for 1·5 years, decreased proteinuria (<8·4 g day^{-1}) and the tibial oedema disappeared. No tumour-associated antigens were present in serum and serological tests for viral infections were negative.

In April 1992, the patient was referred to our institute for further investigation. His body weight was 79 kg and his height 176 cm. Renal function was stable [creatinine: 1·37 mg dL^{-1} (121·1 μmol L^{-1})] and proteinuria was 6·4 g day^{-1}. Serum protein was slightly decreased (50 g L^{-1}) and plasma albumin was 2·15 g dL^{-1}. Haematological indices remained within normal ranges. Plasma viscosity (1·64 mPa s; reference 1·24 ± 0·1 mPa s), concentrations of fibrinogen (0·78 g dL^{-1}, 22·9 μmol L) and α_2-macroglobulin (4·7 g L^{-1}) were increased. Hypercholesterolaemia persisted at 439 mg dL^{-1} (11·3 mmol L^{-1}) and coronary angiography revealed a severe three-vessel disease. Coronary bypass surgery was performed in October 1992.

Both parents of the patient died at the age of 70 without history of coronary artery disease. One of his two brothers is suffering from a peripheral artery disease. The other brother and his sister have no clinical symptoms of atherosclerosis. Both of his daughters are clinically healthy with normal plasma values for cholesterol, triglycerides, LDL and HDL concentrations, but revealed elevated Lp(a) concentrations of 60 and 70 mg dL^{-1} (0·6 and 0·7 g L^{-1}). His wife is normocholesterolaemic and her Lp(a) concentration is 2·9 mg dL^{-1} (0·029 g L^{-1}).

Chemical and lipoprotein determinations

Clinical chemistry and immunological indices were measured by standard techniques. Plasma cholesterol and triglycerides were measured using enzymatic test kits from Boehringer (Mannheim, Germany). Serum LDL-cholesterol was quantified by a direct precipitation procedure (Immuno, Heidelberg, Germany) [9]. As both LDL and Lp(a) are precipitated by this procedure, the true LDL-cholesterol value was calculated by subtracting the corresponding Lp(a) concentration multiplied by 0·3 [Lp(a)-cholesterol] [3]. The concentration of serum Lp(a) was determined by Laurell electrophoresis using commercial antibodies from Immuno. Apo(a) isoforms were characterized by Dr Uterman, University of Innsbruck, Austria.

HDL-cholesterol was measured enzymatically (Boehringer Mannheim) after initial precipitation of

Table 1. Laboratory data of the nephrotic patient

	Reference	Status of nephrotic syndrome	1 year after improvement of the nephrotic syndrome	
Clinical chemistry				
Sodium	135–155	137	142	mmol L^{-1}
Potassium	3·5–5·0	3·5	4·5	mmol L^{-1}
Calcium	2·05–2·65	8·1	9·4	mg dL^{-1} [1]
Creatinine	0·5–1·2	1·37	1·27	mg dL^{-1} [2]
Blood urea nitrogen	9–50	42·8	42·4	mg dL^{-1} [3]
Uric acid	3·5–7·0	8·0	8·0	mg dL^{-1} [4]
Protein, total	6·0–8·0	5·0	7·0	g dL^{-1} [5]
Albumin	3·5–5·0	2·15	4·6	g dL^{-1} [5]
Fibrinogen	0·16–0·40	0·78	0·44	g dL^{-1} [6]
Plasma viscosity	1·18–1·31	1·64	1·26	mPa s
Lipids and lipoproteins				
Cholesterol, total	140–240	439	210	mg dL^{-1} [7]
Triglycerides	70–250	219	123	mg dL^{-1} [8]
VLDL-cholesterol	5–40	37	9	mg dL^{-1} [7]
LDL-cholesterol	90–190	191	97	mg dL^{-1} [7]
HDL-cholesterol	35–75	54	48	mg dL^{-1} [7]
Apolipoprotein B	70–150	290	126	mg dL^{-1} [5]
Apolipoprotein A1	100–180	170	142	mg dL^{-1} [5]
Lipoprotein (a)	<30	470	169	mg dL^{-1} [5]
Lp (a) cholesterol		157	56	mg dL^{-1} [7]
Urinary protein	<30	6400	1800	mg day^{-1} [9]

Factors for conversion to SI units: [1] F = 0·25 (mmol L^{-1}). [2] F = 88·4 (μmol L^{-1}). [3] F = 0·357 (mmol L^{-1}). [4] F = 59·48 (μmol L^{-1}). [5] F = 10 (g L^{-1}). [6] F = 29·4 (μmol L^{-1}). [7] F = 0·0256 (mmol L^{-1}). [8] F = 0·0113 (mmol L^{-1}). [9] F = 0·001 (g day^{-1}).

Apo B-containing lipoproteins with phosphotungstate/$MgCl_2$. The apoproteins B and A1, as well as fibrinogen, were quantified by rate nephelometry using commercial antibodies from Behring (Marburg, Germany). Plasma viscosity was determined by capillary viscometry [12]. LDL receptor activity was assayed in cultured skin fibroblasts as described previously [13].

Post apheresis reaccumulation of LDL, Lp(a) and fibrinogen

A single HELP apheresis was performed in July 1992 to prove the efficacy of this procedure in removal of plasma Lp(a) and to determine the reaccumulation rates of LDL, Lp(a) and plasma fibrinogen in patients with nephrotic syndrome [9,10]. The apparatus used, a Plasmat Secura, was provided by B. Braun (Melsungen, Germany). A total of 3 L of plasma was treated. Plasma and serum samples were obtained directly before and after the HELP apheresis. During the subsequent 7 days, blood samples were taken daily to follow the post treatment return of lipoproteins and fibrinogen to their baseline levels. The fractional catabolic rates (FCRs) of LDL, Lp(a) and fibrinogen were calculated as described by Apstein *et al.* [11]. This calculation model was used under the assumption that the synthesis and FCR of lipoproteins are not affected by rapid changes in the pool size [11,14]. The plasma volume was taken as 4·5% of body weight. The pool size was calculated by multiplying the plasma concentration with the plasma volume. The synthetic rate was estimated as the product of FCR and plasma pool size expressed per kilogram of body weight [15].

Results

Plasma protein and lipoprotein concentrations in the patient during the clinical phase of nephrotic syndrome and after improvement of the renal function are presented in Table 1. In the nephrotic state, severe hypercholesterolaemia was accompanied with very high total plasma Lp(a) concentrations of 470 mg dL^{-1} [4·7 g L^{-1}; Lp(a)-cholesterol concentrations of 141 mg dL^{-1}] and high plasma fibrinogen (780 mg dL^{-1}, 7·8 g L^{-1}). The plasma LDL-cholesterol level was 191 mg dL^{-1} (4·9 mmol L^{-1}). Plasma triglycerides were slightly increased to 219 mg dL^{-1} (2·5 mmol L^{-1}), whereas the VLDL- and HDL-cholesterol levels were within the normal range. Plasma albumin concentration was decreased (2·15 g dL^{-1}) and urinary protein loss was 6·4 g day^{-1}. LDL receptor activity in cultured skin fibroblasts of the patient and his family was similar to normolipidaemic control subjects. With the normalization of hypoalbuminaemia and proteinuria, the plasma Lp(a) concentrations decreased to 169 mg dL^{-1} [Lp(a)-cholesterol 50·7 mg dL^{-1}], and the LDL-cholesterol concentration to about 100 mg dL^{-1}. The course of plasma Lp(a), albumin and urinary protein is shown in Fig. 1. Fibrinogen remained elevated above 400 mg dL^{-1} (0·4 g dL^{-1}). The apoprotein(a) isoform patterns are shown in Table 2. The patient and his daughter displayed the same small isoform S2 and a common allele 10.

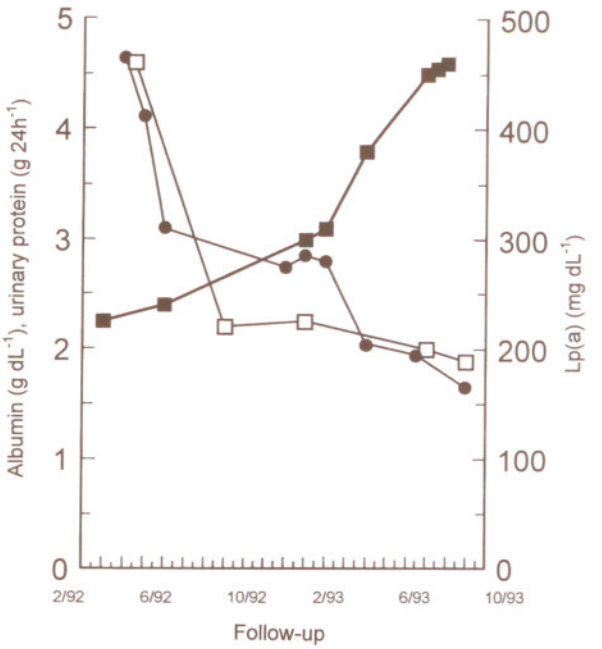

Figure 1. Changes in LDL cholesterol, lipoprotein (a) (●), albumin (■) and urinary protein (□) after clinical diagnosis of nephrotic syndrome.

The effects of the HELP apheresis (1 h and 7 days post apheresis) on the elimination of LDL, Lp(a) and fibrinogen are presented in Table 3. The post-apheresis return of LDL, Lp(a) and fibrinogen to baseline levels in the nephrotic patient, FH heterozygote and normolipidaemic control are illustrated in Fig. 2. Post-apheresis return of LDL-cholesterol and Lp(a) in the nephrotic was delayed as compared with the control but was similiar to hypercholesterolaemic subjects. Calculation of turnover rates for LDL-cholesterol, Lp(a) and fibrinogen are presented in Table 4. The FCR for LDL-cholesterol was greatly reduced in our nephrotic patient, but was similar to the FH heterozygote patient. In contrast, absolute catabolic rates (ACRs) for the normolipidaemic

Table 2. Apoprotein (a) isoforms in the patient and his family

	Lp(a) mg dL^{-1}	Apo(a) isoforms*	Alleles 1 and 2*
Patient (D.K.)	470	S2	10 and 19
Patient's daughter (D.P.)	60·2	S2	10 and 16
Patient's wife (D.S.)	2·9	S2 S4	16 and 22

* Kindly performed by Dr G. Utermann, University of Innsbruck, Austria.

Table 3. Elimination and reaccumulation of lipoproteins and plasma fibrinogen in the nephrotic patient after HELP apheresis

		Before HELP	One hour after HELP	Reduction (%)	Seven days after HELP	Reduction (%)
Cholesterol, total	mg dL^{-1} [1]	345	155	−55	242	−30
Triglycerides	mg dL^{-1} [2]	234	109	−53	128	−45
LDL-cholesterol	mg dL^{-1} [1]	159	57	−64	102	−36
HDL-cholesterol	mg dL^{-1} [1]	47	38	−19	49	+4
Apolipoprotein A1	mg dL^{-1} [3]	150	124	−17	130	−13
Apolipoprotein B	mg dL^{-1} [3]	222	86	−61	156	−30
Lipoprotein (a)	mg dL^{-1} [3]	320	120	−62	220	−31
Fibrinogen	g dL^{-1} [4]	0·937	0·458	−51	0·870	−7
Plasma viscosity	mPa s	1·39	1·10	−21	1·32	−5

Factors for conversion to SI units: [1] F = 0·0256 (mmol L^{-1}). [2] F = 0·0113 (mmol L^{-1}). [3] F = 10 (g L^{-1}). [4] F = 29·4 (μmol L^{-1}).

Table 4. Turnover data calculated from reaccumulation (7 days) after HELP apheresis

	Normolipidaemic control	Familial hypercholesterolaemia (heterozygous)	Nephrotic patient
LDL-C before HELP (mg dL^{-1})	128	270	159
FCR (pools day^{-1})	0·430	0·190	0·133
Absolute clearance rate (mg kg^{-1} day^{-1})	24·7	23·11	9·5
Lp(a) before HELP (mg dL^{-1})	65	107	320
FCR (pools day^{-1})	0·199	0·162	0·105
Absolute clearance rate (mg kg^{-1} day^{-1})	5·8	7·8	15·2
Fibrinogen before HELP	–	306	937
FCR (pools day^{-1})	–	0·188	0·20
Absolute clearance rate (mg kg^{-1} day^{-1})	–	25·9	84·3

The fractional catabolic rates (FCRs) for LDL, Lp(a) and fibrinogen were calculated on the basis of the corresponding kinetic post-apheresis values according to Apstein *et al.* [11] $\{\ln[(\text{conc}_o - \text{conc}_t)$ divided by $(\text{conc}_o - \text{conc}_{min})] = -kt\}$. Conc_o is the initial steady-state plasma concentration before HELP, conc_{min} is the concentration directly after HELP and conc_t is the concentration at time t after cessation of HELP. Constant k is a first-order disappearance constant. Least-square regression through $-kt$ of days 1–7 (slope) yields the FCR of the investigated plasma protein.

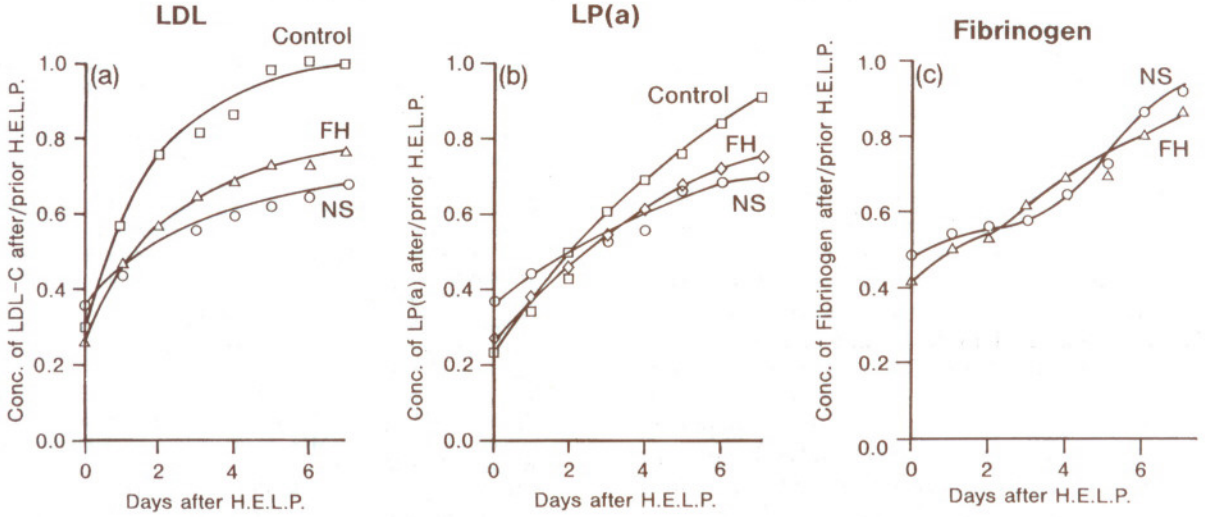

Figure 2. Post HELP apheresis return to basal plasma levels of LDL cholesterol (a), lipoprotein(a) (b) and fibrinogen (c) in a patient suffering from nephrotic syndrome. Conc.post/prior HELP represents the plasma concentration at time t (days after HELP apheresis), divided by the pretreatment concentration. The reaccumulation data are compared with a normolipidaemic subject (LDL cholesterol 128 mg dL^{-1}, Lp(a) 65 mg dL^{-1}) and a patient suffering from familial hypercholesterolemia (LDL cholesterol 270 mg dL^{-1}, Lp(a) 107 mg dL^{-1}), both showing normal renal function [9].

control and FH heterozygote were similar, but the ACR for LDL in the nephrotic patient was reduced. The FCR for Lp(a) in the nephrotic patient was reduced in comparison to the normolipidaemic control as well as the FH heterozygote patient, whereas ACR for Lp(a) in the nephrotic patient was increased. This can probably be explained on the basis of a shift of apolipoprotein B towards increased Lp(a) rather than LDL production. Although the absolute synthesis rate of fibrinogen in the nephrotic patient was increased, the FCR was similar to those in the non-nephrotic hypercholesterolaemic patient.

As plasma Lp(a) and fibrinogen levels remained elevated even 1 year after clinical improvement in the nephrotic syndrome, we started regular HELP treatment at weekly intervals. The average interval concentrations between two treatments of LDL-cholesterol, Lp(a) and fibrinogen are now maintained at 60 mg dL^{-1}, 85 mg dL^{-1}, and 215 mg dL^{-1} respectively.

Discussion

Mechanisms causing hyperlipidaemia in patients with nephrotic syndrome are still unclear. Increased plasma LDL concentrations in nephrotic patients have been attributed to either overproduction or decreased catabolism, or both [15–17]. Furthermore, *in vitro* studies have demonstrated that altered lipid protein composition of LDL (i.e. triglyceride-rich core) are poor ligands for LDL receptors. Such triglyceride-rich lipoprotein particles are a regular feature of these patients and may explain their decreased catabolic rate. It has also been reported that nephrotic patients have reduced renal clearance of plasma mevalonate, a metabolite reported to suppress the LDL receptor activity. A reduced renal clearance of plasma mevalonate, which has been reported in these patients, may increase hepatic intracellular sterols and thereby suppress LDL receptor activity [16]. However, studies on FCRs in nephrotic patients are controversial because some studies report normal clearance of LDLs whereas others report reduced clearance in nephrotic patients [15,16].

Our nephrotic syndrome patient had elevated total plasma cholesterol but normal VLDL- and HDL-cholesterol levels. Both the plasma LDL-cholesterol and triglycerides were in the upper range for normolipidaemic healthy controls. However, his plasma Lp(a) levels and fibrinogen values were over 15-fold and two-fold higher than the normal healthy controls. There are only a few studies that report Lp(a) levels in patients with nephrotic syndrome. In a recent study, 9 from a total of 11 patients with primary nephrotic syndrome displayed elevated Lp(a) levels [4]. No correlation between Lp(a) concentration and proteinuria, hypoalbuminaemia, LDL-cholesterol and Lp(a) size polymorphism could be established.

The plasma Lp(a) concentration in our nephrotic patient is to our knowledge the highest reported in the literature so far. After clinical improvement in the nephrotic syndrome, Lp(a) concentrations decreased from 470 mg dL^{-1} to 169 mg dL^{-1}. This decrease was associated with a constant elevation of serum albumin. Analysis of apo(a) isoforms in the patient and his daughter revealed that both shared a common allele 10, which was responsible for the elevated Lp(a) levels in the daughter. The other alleles, 19 in the father and 16 in the daughter, are unlikely to cause an increase in Lp(a). Comparing the Lp(a) concentrations of our patient with his daughter, the presence of allele 10 does not explain his extremely high Lp(a) levels. It thus appears that this elevation is secondary and may result from the nephrotic syndrome. However, it is worth noting that even 1 year after the improvement in his nephrotic symptoms the Lp(a) values remained twofold higher than in his daughter. This difference cannot solely be explained on the basis of apo(a) genotype.

Consequently as a therapeutic strategy, elevated Lp(a) and fibrinogen levels should both be normalized in patients with nephrotic syndrome and small apo(a) isoforms. For this purpose, extracorporeal HELP apheresis is the only promising regimen available at present.

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