European Journal of Clinical Investigation (1989) **19**, 235–240

Effect of HELP-LDL-apheresis on serum concentrations of human lipoprotein(a): kinetic analysis of the post-treatment return to baseline levels

V. W. ARMSTRONG, J. SCHLEEF*, J. THIERY, R. MUCHE, P. SCHUFF-WERNER, T. EISENHAUER† & D. SEIDEL, Departments of Clinical Chemistry, * Surgery and † Nephrology, University Hospital, Robert-Koch-Str. 40, D-3400 Göttingen, FRG

Received 1 August and in revised form 20 December 1988

Abstract. In addition to LDL, Lp(a) can be quantitavely eliminated from plasma in an extracorporeal LDL-apheresis procedure based on precipitation with heparin at pH 5·12. The rates of return of post-apheresis Lp(a) and LDL-cholesterol concentrations to baseline levels were investigated in six individuals with familial hypercholesterolaemia (one homozygote, five heterozygote) and one normolipaemic individual. The first-order disappearance constants (k) were derived for LDL and Lp(a) according to Apstein *et al.* [1]. The k values for LDL in the homozygous FH and the normolipaemic individual were 0·082 and 0·43 respectively while the heterozygous FH patients had k values intermediate between the two (median 0·231; range 0·116–0·261). The first-order disappearance constants of Lp(a) did not correlate with those of LDL. The homozygous FH and normolipaemic individuals had Lp(a) k values of 0·158 and 0·199 respectively; the corresponding values in the heterozygous FH patients were: median 0·142; range 0·045–0·179.

Keywords. FCR, LDL-apheresis, lipoprotein (a), familial hypercholesterolaemia.

Introduction

High plasma concentrations of the lipoprotein Lp(a) are strongly associated with an increased incidence of coronary heart disease [2–6]. The structure of Lp(a) is essentially that of an LDL particle to which the glycoprotein apo(a) is attached through disulphide bridges to apo B-100 [7–9]. Apo(a) exhibits an unusual polymorphism and several different molecular weight isoforms have been identified. This polymorphism appears to be coded for by a series of codominant alleles at a single gene locus [10–12]. Recently both classical protein sequencing studies [13–14] and analysis of the cDNA sequence coding for apo(a) [15] have revealed a high homology between apo(a) and human plasminogen. The complete sequence of an apo(a) isoform derived from its cDNA has been described by McLean *et al.* [15]. It consists of a series of 37 kringle domains, homologous to the kringle 4 region of plasminogen followed by one copy each of a kringle 5 and an inactive serine protease domain; kringles homologous to kringles 1, 2 and 3 of plasminogen have not been retained in apo(a). The polymorphism of apo(a) is presumed to be due to differences in the number of kringle 4 domains.

Of all the plasma lipids and lipoproteins, Lp(a) demonstrates the highest heritability and plasma concentrations are under stringent genetic control [16]. These concentrations are refractory to diet [17] and are generally unaffected by most cholesterol-lowering drugs. Bile-acid binding resins such as cholestyramine [18] or HMG-CoA-reductase inhibitors such as simvastatin [19] do not alter plasma Lp(a) levels at doses which bring about an effective reduction in LDL-cholesterol concentrations. Modest decreases in Lp(a) levels have, however, been observed in some individuals on treatment with neomycin and niacin, particularly when used in combination [20]. The anabolic steroid stanozolol has also been shown to reduce plasma Lp(a) concentrations [21].

In an earlier observation [22] we had noted that plasma Lp(a) concentrations could be lowered by an extracorporeal LDL-apheresis procedure based on the heparin-induced precipitation of LDL at low pH (HELP). In view of the apparent resistance of Lp(a) to both dietary and drug treatment, we have now studied in greater detail the elimination of Lp(a) through HELP-LDL-apheresis paying particular attention to the kinetics of the return to the original baseline concentrations.

This work is dedicated to Prof. Werner Creutzfeldt, Department of Internal Medicine, University of Göttingen on the occasion of his 65th birthday.

Correspondence: Dr V. W. Armstrong, Department of Clinical Chemistry, University Hospital, Robert-Koch-Str. 40, D-3400 Göttingen, FRG.

Table 1. Clinical and laboratory data of the individuals included in this study

Subject	M/F	Age	LDL-receptor status	Serum cholesterol (mmol l^{-1})	Serum triglycerides (mmol l^{-1})	Serum LDL-cholesterol (mmol l^{-1})	Serum Lp(a) (mg dl^{-1})
1	F	7	FH homozygous	22·37	1·62	19·92	98
2	M	32	FH heterozygous	11·61	3·94	7·98	81
3	M	37	FH heterozygous	10·49	2·67	8·19	21
4	M	37	FH heterozygous	9·31	1·00	7·08	107
5	F	43	FH heterozygous	9·41	2·18	6·12	75
6	M	45	FH heterozygous	7·46	1·90	4·87	105
7	F	45	Normal	5·82	0·86	3·32	65

Materials and methods

Subjects

Seven individuals were included in this study (Table 1). One individual (subject 1) is a young girl with homozygous familial hypercholesterolaemia (FH), documented by tissue culture to be of the receptor-defective type. She has now been on regular treatment with HELP-LDL-apheresis for over 2 years. A further five individuals (subjects 2–6) are suffering from the heterozygous form of FH, as revealed from tissue culture studies and/or family histories; they are part of a larger collective of patients with type II hypercholesterolaemia and coronary artery disease currently being treated with HELP. The seventh individual was a normocholesterolaemic volunteer included for comparison purposes. All probands were selected for this present study on the basis of their high (>20 mg dl^{-1}) concentrations of Lp(a).

Therapy with lipid-lowering drugs was discontinued 4 weeks prior to investigating the effect of a single apheresis treatment on serum LDL-cholesterol and Lp(a) concentrations. Written consent was obtained from all individuals prior to beginning this study. The approval of the local university ethics committee was also obtained.

LDL-apheresis

The procedure for HELP-LDL-apheresis has been described in detail elsewhere [22]. In the case of adults, 3000 ml of plasma were normally treated at one session, treatment time lasting approximately 2 h. For the homozygous child we initially began treating 1000 ml of plasma; this was increased to 1500 ml after approximately 1 year of regular treatment.

Blood samples were taken directly before and after each LDL-apheresis. For the kinetic study samples were also taken at 24 h intervals subsequent to the apheresis for a period of 5–7 days, in order to follow the return of the various lipoproteins and apolipoproteins to their pretreatment values.

Analytical procedures

Lp(a) was quantified by means of a non-competitive enzyme-linked immunosorbent assay (ELISA). A polyclonal antiserum was raised in rabbits immunized with Lp(a). After removal of B-100 antibodies by immunosorbtion over LDL-sepharose, immunoglobulins (IgG) were separated from other serum proteins over Protein-A-Sepharose. Microtitre plates (NUNC) were coated with anti-Lp(a) IgG (0·05 μg protein $well^{-1}$) in an overnight incubation at 4°C and pH 10·4. After washing and blocking for 1 h with 1% (w/v) gelatine, 0·1 ml of appropriately diluted Lp(a) standards or serum samples were incubated in the wells for 2 h at room temperature. The wells were then washed and biotin-labelled anti-Lp(a) IgG (1·4 μg protein $well^{-1}$) was added to each well and incubation continued for a further hour at room temperature. After washing, the wells were then incubated with a biotinylated streptavidin peroxidase conjugate (Amersham) for 30 min. Finally a freshly prepared solution of 0·4 mM Azino-di(3-ethylbenthiazolinsulphonic acid) and 0·01% H_2O_2 was added; colour development was stopped after 15 min with an equal volume of 1 N H_2SO_4 and the plate read at 410 nm. Cross reactivity with human plasminogen was $<0·02$% using this assay.

Total cholesterol and total triglycerides were quantified using enzymatic test kits (Boehringer, Mannheim, FRG). Serum LDL-cholesterol was measured by a precipitation procedure [23] using dextran sulphate (Quantolip-LDL, Immuno, Heidelberg, FRG). Since both LDL and Lp(a) are precipitated under the conditions of this assay [23], the LDL-cholesterol value obtained from this procedure will also include that cholesterol contained in Lp(a). The true LDL-cholesterol value can be calculated by subtracting the corresponding Lp(a) lipoprotein concentration $\times$ 0·3 [2,3]. HDL-cholesterol was measured by the phosphotungstate/$MgCl_2$ procedure (Boehringer, Mannheim, FRG). The apoproteins B and A-I were quantified using rate nephelometry [24].

Results

The extent to which a protein or lipoprotein is eliminated during apheresis depends upon the efficiency of its removal, the volume of plasma treated, and the total plasma volume of the individual [25].

Table 2. Effect of a single HELP treatment on serum LDL-cholesterol, HDL-cholesterol, Lp(a), apoB and apoA-1 concentrations

	LDL-c (mmol l^{-1})			Lp(a) (mg dl^{-1})			apoB (mg dl^{-1})			HDL-c (mmol l^{-1})			ApoA-1 (mg dl^{-1})		
	C_o	CM	CM/C_o	C_o	CM	CM/C_o	C_o	CM	CM/C_o	C_o	CM	CM/C_o	C_o	CM	CM/C_o
1	19·92	6·18	0·32	98	40	0·41	364	151	0·42	0·57	0·23	0·40	29	10	0·35
2	7·98	3·88	0·49	81	43	0·53	231	107	0·46	1·55	1·24	0·80	187	143	0·77
3	8·19	3·63	0·44	21	10	0·48	179	96	0·54	0·93	0·85	0·91	71	51	0·72
4	7·08	1·82	0·26	107	25	0·23	172	58	0·34	1·06	0·72	0·68	86	63	0·73
5	6·12	2·02	0·33	75	33	0·44	160	70	0·44	1·24	1·06	0·85	125	110	0·88
6	4·87	1·81	0·37	105	30	0·29	173	76	0·44	1·27	1·11	0·87	115	88	0·77
7	3·32	1·05	0·32	65	18	0·28	120	46	0·38	1·53	1·42	0·93	124	91	0·73
x			0·36			0·38			0·43			0·77			0·71
(SD)			(0·08)			(0·11)			(0·06)			(0·19)			(0·17)

C_o: Steady-state serum concentration immediately prior to the HELP treatment.
CM: Serum concentration immediately after the HELP treatment.

Since we have previously demonstrated [22] that LDL are completely eliminated in an extracorporeal LDL-apheresis procedure based on their heparin-induced precipitation at pH 5·12 we compared the elimination of Lp(a) to that of LDL-cholesterol by a single HELP-LDL-apheresis. In addition, the corresponding concentrations of apoB, apoA-1 and HDL-cholesterol were determined. The effects of a single HELP-LDL-apheresis on serum concentrations of LDL-cholesterol, Lp(a), apoB, HDL-cholesterol and apoA-1 in all seven subjects studied are presented in Table 2. The ratios of the post-treatment to pretreatment values are included to allow a comparison of the efficiency of removal of the various lipoproteins and apoproteins.

The mean ratio for LDL-cholesterol was 0·36 and that for Lp(a) was 0·38; in other words LDL-cholesterol and Lp(a) levels were reduced by an average of 64% and 62% respectively through a single HELP-LDL-apheresis. There was a good correlation ($r=0·84$, $y=0·71x+0·09$) between the individual ratios indicating that LDL and Lp(a) are eliminated to the same extent. As would be expected, the ratios for apoB were similar to those for LDL-cholesterol and Lp(a). With the exception of the homozygote, whose basal levels were very low prior to apheresis, only minor decreases were observed in HDL-cholesterol and apoA-1 after apheresis. These findings are consistent with our previous observations that HDL are not precipitated

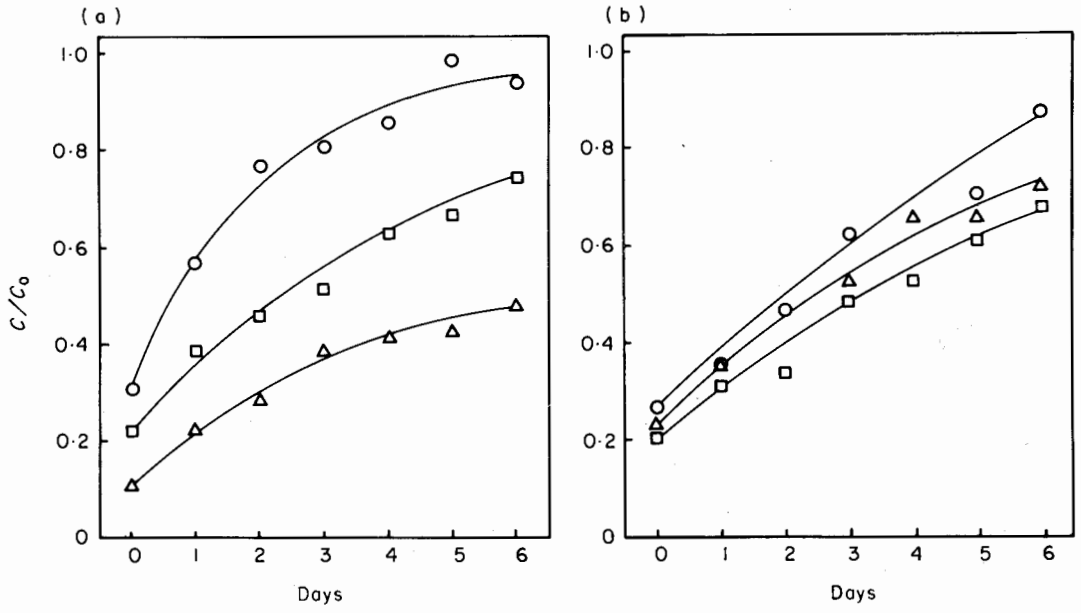

Figure 1. Post-treatment return to basal levels of (a) LDL-cholesterol and (b) Lp(a) in: O—O a normolipaemic individual; □—□ an individual with heterozygous FH; and, Δ—Δ an individual with homozygous FH. C represents the serum concentration at time t days after the last apheresis and C_o represents the pretreatment concentration.

by heparin under the conditions of the HELP procedure [21–26].

The return of both LDL-cholesterol and Lp(a) concentrations to pretreatment levels was followed over a period of 5–7 days. In Fig. 1, the rate of return to baseline levels of both Lp(a) and LDL-cholesterol is illustrated for three individuals with different LDL-receptor activities. In the case of the normocholesterolaemic individual, the post-treatment LDL-cholesterol concentration rapidly returned towards the steady-state pretreatment level of 3·32 mmol l^{-1} whereas a relatively slower rate was observed in the homozygous child who had a pretreatment LDL-cholesterol level of 19·92 mmol l^{-1} (Fig. 1a). An individual with the heterozygous form of FH displayed a rate of return of LDL-cholesterol that was intermediate between those of the normocholesterolaemic and the homozygous individuals.

The situation for Lp(a) was, however, quite different to that for LDL. Despite the differences in their LDL-receptor status, all three individuals showed similar rates of return of their Lp(a) levels to pretreatment values (Fig. 1b).

Apstein *et al.* [1] have previously shown that the rate of return of plasma cholesterol to pretreatment cholesterol concentrations after sustained plasmapheresis can be predicted from the equation:

$$\ln\frac{C_o - C}{C_o - CM} = -kt$$

where C_o is the initial steady-state cholesterol concentration prior to plasmapheresis, CM is the minimum cholesterol level after plasmapheresis and C is the cholesterol concentration at time t after cessation of plasmapheresis. The constant k is then the first-order disappearance constant for plasma lipoprotein cholesterol, or in other words the fractional catabolic rate (FCR) of plasma cholesterol. Although this calculation assumes that both the synthetic and fractional catabolic rates of plasma cholesterol remain constant after a decrease in pool size through plasmapheresis, reasonable agreement was found between the FCR determined from the above equation and that obtained for LDL-apoB from steady-state isotopic studies. We therefore employed the above equation to derive the first-order disappearance constant k for both LDL-cholesterol and Lp(a) in all seven individuals. Least squares regression analyses were carried out on the corresponding kinetic data and the results are presented in Table 3. As would be expected the lowest k value of 0·082 for LDL-cholesterol was observed for the homozygous child. This value is similar to those values reported by Apstein *et al.* [1] for two homozygotes. Although the latter values were obtained for the return of total cholesterol to baseline levels, LDL-

Table 3. First-order disappearance constants (k) in response to HELP-LDL-apheresis for LDL and Lp(a) in seven individuals

	k	
Subject	LDL	Lp(a)
1	0·082	0·158
2	0·166	0·142
3	0·116	0·045
4	0·231	0·162
5	0·235	0·179
6	0·261	0·135
7	0·430	0·199

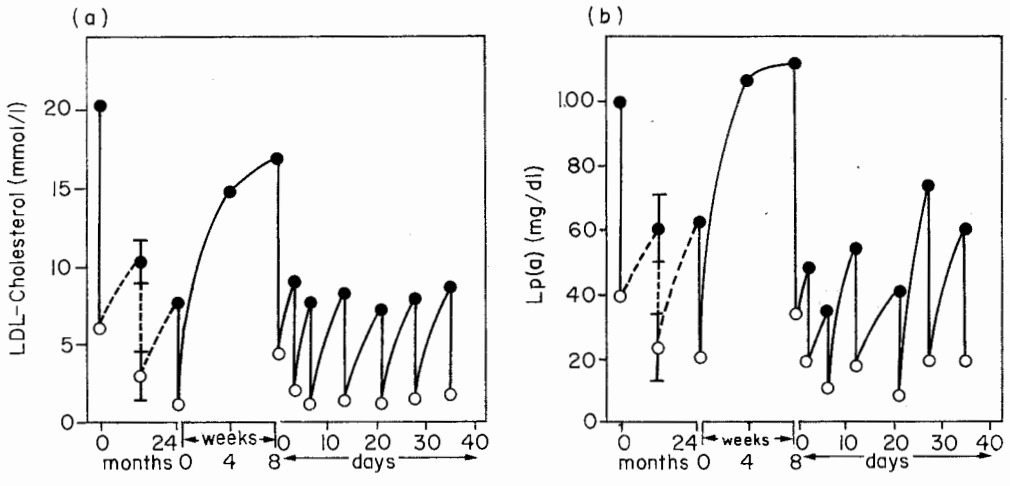

Figure 2. Course of (a) serum LDL-cholesterol and (b) serum Lp(a) concentrations in a homozygous child during regular HELP-LDL-apheresis therapy. Pre-apheresis values are illustrated by closed circles (●) and postapheresis values by open circles (○). During the first 2 years of treatment a total of 90 aphereses were performed. The individual data from the first and last aphereses in this period are presented together with the mean values from the remaining treatments ($n = 88$). There then followed an apheresis-free interval in which serum LDL-cholesterol and Lp(a) concentrations were controlled after 4 weeks. Regular treatment was again resumed after 8 weeks and the results from a further seven individual aphereses are presented.

cholesterol makes the largest contribution to total cholesterol. The k values of LDL-cholesterol in the five heterozygous individuals are in the same range as the FCRs reported for LDL-apoB from radiolabelling studies [27]. As would be expected the normocholesterolaemic individual displayed the higher value for the first-order disappearance constant of LDL-cholesterol.

The k values of Lp(a) did not correlate with those of LDL-cholesterol. Although the homozygous child and the normocholesterolaemic individual displayed a four-fold difference in their LDL-cholesterol k values, there was only a small difference between the Lp(a) k values of these individuals. With the exception of the homozygote the k values of Lp(a) were lower than those of LDL-cholesterol and averaged 60% of the latter.

We have now been able to follow the effect of long-term repetitive HELP-LDL-apheresis on serum Lp(a) and LDL-cholesterol concentrations in the homozygous child for a period of over 2 years. This child is being regularly treated at weekly intervals with the exception of holidays and illness. During the first 2 years of regular HELP treatment, the mean pre-apheresis LDL-cholesterol concentration was around 50% of the initial pretherapeutic value of 19·92 mmol l^{-1} (Fig. 2). Serum Lp(a) concentrations could also be maintained at a reduced level, the mean pre-apheresis value being 61% of the original steady-state concentration. After 2 years of treatment there was an apheresis-free period due to holiday. During the first 4 weeks of this period Lp(a) concentrations had returned to their original, baseline level whereas the LDL-cholesterol concentration had attained only 72% of its original pretreatment level. After resumption of apheresis-treatment serum LDL-cholesterol and Lp(a) concentrations could once again be lowered to levels similar to those observed during the first 2 years of treatment.

Discussion

In addition to LDL and a limited number of other heparin binding proteins such as fibrinogen [22,26] the lipoprotein Lp(a) is also quantitatively eliminated from plasma in an extracorporeal apheresis procedure based on precipitation with heparin at acidic pH. This is consistent with the observation that Lp(a) can also bind to proteoglycans such as heparin this binding being mediated by the apoB moiety of Lp(a) and not by apo(a) [9].

Apstein *et al.* have previously demonstrated [1] that the rate at which plasma cholesterol levels return to pretreatment values after sustained plasmapheresis can be employed to derive the first-order disappearance constant (FCR) of cholesterol. This was based on the assumption that the production rate for LDL remains constant after plasmapheresis and that the FCR is proportional to the plasma cholesterol concentration irrespective of pool size. Thompson *et al.* [28,29] were able to demonstrate by plasma exchange that the FCR of LDL in FH is indeed independent of pool size irrespective of whether the individuals studied were homozygous or heterozygous. Furthermore, the studies of Soutar *et al.* [30] showed that LDL-apoB synthesis did not increase after plasma exchange in both homozygous and heterozygous FH patients. A short-term decrease in the LDL-pool does not therefore alter the synthesis or FCR of this lipoprotein even in those individuals possessing LDL-receptor activity. These results confirm the assumptions of Apstein *et al.*, at least as far as homozygous and heterozygous FH subjects are concerned.

In this investigation we compared the rates of return to post-treatment levels of Lp(a) and LDL after an acute reduction in their pool size due to removal by apheresis. We employed the model of Apstein *et al.* for this purpose which necessarily requires the assumption that the synthesis and FCR of Lp(a) are not affected by changes in pool size. It was of particular interest to compare the rates of return of post-apheresis Lp(a) and LDL-cholesterol concentrations in persons with clinically documented differences in LDL-receptor status. The rates of return of LDL-cholesterol were clearly different in a homozygous FH, a heterozygous FH and a normolipaemic individual the calculated first-order disappearance constants being 0·082, 0·166 and 0·430 respectively. These three individuals did not, however, display any major differences in the rates of return of their Lp(a) concentrations to basal levels, the corresponding first-order disappearance constants being 0·158, 0·142 and 0·199 for the homozygote, heterozygote and normolipaemic subjects respectively. The data are consistent with the hypothesis that Lp(a) are not cleared to any great extent by the LDL-receptor pathway *in vivo*. This is supported by the observation that Lp(a) concentrations are unaffected by bile acid sequestrants such as cholestyramine [18] and HMG CoA-reductase inhibitors such as simvastatin [19], drugs that effectively lower LDL-cholesterol levels by raising LDL-receptor activity. Although several *in vitro* studies [9,31–33] on cultured human fibroblasts have indicated that Lp(a) can be bound, internalized and finally degraded through the LDL-receptor pathway, Lp(a) is a much poorer ligand for the receptor than LDL itself [9,34]. Only after removal of the apo(a) by disulphide reduction does the residual lipoprotein Lp(a) show similar affinity to the LDL-receptor as LDL [9].

Krempler *et al.* [33] studied the *in vivo* removal of radioiodinated Lp(a) in 12 normolipaemic individuals and found a highly significant correlation between the FCRs of Lp(a) and LDL, the mean value for Lp(a) being approximately 30% lower than that of LDL. However, they did include one patient with homozygous FH in this investigation. Interestingly the FCR for Lp(a) in this individual was higher than the corresponding FCR for LDL, the former being only 81% of the mean Lp(a) FCR in normal subjects while the latter was 54% of the mean value in normal controls. In order to fully clarify the role of the LDL-

receptor pathway in the catabolism of Lp(a), turnover studies are obviously required in a larger number of persons with different LDL-receptor activities.

In view of the fact that a combination of elevated LDL-cholesterol concentrations and high Lp(a) levels are associated with a high coronary risk [4], the simultaneous elimination of these two lipoproteins must be considered as an additional benefit of this apheresis system. However, further knowledge of the causal relationship between Lp(a) and the development of atherosclerosis is required before the therapeutic potential of this elimination can be properly assessed.

Acknowledgments

We gratefully acknowledge the expert technical assistance of Margit Stix and Karolin Fuchs. Our thanks are also due to the staff of the HELP-LDL-apheresis unit. We are indebted to Christine Berwanger for secretarial assistance in the preparation of this manuscript. This work was supported by a grant from the Deutsche Forschungsgemeinschaft.

References

1 Apstein CS, Zilversmith DB, Lees RS, George PK. Effect of intensive plasmapheresis on the plasma cholesterol concentration with familial hypercholesterolemia. Atherosclerosis 1978; 31:105–15.
2 Berg K, Dahlem G, Borresen A-L. Lp(a) phenotypes, other lipoprotein parameters, and a family history of coronary heart disease in middle-aged males. Clin Genet 1979;16:347–52.
3 Kostner GM, Avogara P, Cazzolato G, Marth E, Bittolo-Bon G, Quinci GB. Lipoprotein(a) and the risk of myocardial infarction. Atherosclerosis 1981;38:51–61.
4 Armstrong VW, Cremer P, Eberle E *et al.* The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis. Atherosclerosis 1986;62: 249–57.
5 Rhoads GG, Dhalen G, Berg K, Morten EN, Danneberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. JAMA 1986;256:2540–4.
6 Dahlen G, Guyton JR, Attar M, Famer JA, Kautz JA, Gotto AM. Association of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. Circulation 1986;74:758–65.
7 Uterman G, Weber W. Protein composition of Lp(a) lipoprotein from human plasma. FEBS Letters 1983;154:357–61.
8 Fless GM, ZumMallen ME, Scanu AM. Isolation of apolipoprotein(a) from lipoprotein(a). J Lipid Res 1985;26:1224–9.
9 Armstrong VW, Walli AK, Seidel D. Isolation, characterization and uptake in human fibroblasts of an apo(a)-free lipoprotein obtained on reduction of lipoprotein(a). J Lipid Res 1985; 26:1314–23.
10 Uterman G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes; inheritance and relations to Lp(a) concentration in plasma. J Clin Invest 1987, 80:458–65.
11 Uterman G, Kraft HG, Menzel HJ, Hopferweise T, Seitz C. Genetics of the quantitative Lp(a) lipoprotein trait. I. Relation of Lp(a) glycoprotein phenotypes to Lp(a) lipoprotein concentrations in plasma. Hum Genet 1988;78:41–6.
12 Uterman G, Duba C, Menzel HJ. Genetics of the quantitative Lp(a) lipoprotein trait. II. Inheritance of Lp(a) glycoprotein phenotypes. Hum Genet 1988;78:47–50.
13 Eaton DL, Fless GM, Kohr WJ *et al.* Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. Proc Natl Acad Sci USA 1987;84:3224–8.
14 Kratzin H, Armstrong VW, Niehaus M, Hilschmann N, Seidel D. Structural relationship of an apolipoprotein(a) phenotype (570 kDa) to plasminogen: homologous kringle domains are linked by carbohydrate-rich regions. Biol Chem Hoppe-Seyler 1987;368:1533–44.
15 McLean JW, Tomlinson JE, Kuang WJ *et al.* cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987;300:132–7.
16 Morrisett JD, Guyton JR, Gaubatz JW, Gotto AM. Lipoprotein(a) structure, metabolism and epidemiology. In: Gotto AM, ed. Plasma Lipoproteins. Amsterdam: Elsevier, 1987:129–52.
17 Albers JJ, Cabara VG, Warnick GR, Hazzard WR. Lp(a) lipoprotein: relationship to sinking pre-β-lipoprotein, hyperlipoproteinemia and apolipoprotein B. Metabolism 1975;24: 1047–54.
18 Vessby B, Kostner GM, Lithell H, Thomis J. Diverging effects of cholestyramine on apolipoprotein B and lipoprotein Lp(a). A dose-response study of the effects of cholestyramine in hypercholesterolaemia. Atherosclerosis 1982;44:61–71.
19 Thiery J, Armstrong VW, Schleef J, Creutzfeldt C, Creutzfeldt W, Seidel D. Serum lipoprotein(a) concentrations are not influenced by an HMG CoA reductase inhibitor. Klin Wochenschr 1988;66:462–3.
20 Guraker A, Hoeg JM, Kostner G, Papadopoulos NM, Brewer HB. Levels of lipoprotein(a) decline with neomycin and niacin treatment. Atherosclerosis 1985;57:293–301.
21 Albers J, Taggart HM, Appelbaum-Bowden O, Haffner S, Chesnut CH, Hazzard WR. Reduction of lecithin-cholesterol acyltransferase, apolipoprotein D and the Lp(a) lipoprotein with the anabolic steroid stanozolol. Biochim Biophys Acta 1984;759:293–6.
22 Eisenhauer T, Armstrong VW, Wieland H, Fuchs C, Scheler F, Seidel D. Selective removal of low density lipoproteins (LDL) by precipitation at low pH: first clinical application of the HELP system. Klin Wochenschr 1987;65:161–8.
23 Armstrong VW, Seidel D. Evaluation of a commercial kit for the determination of LDL-cholesterol in serum based on precipitation of LDL with dextran sulfate. Ärzt Lab 1985;31:325–30.
24 Wieland H, Cremer P, Seidel D. Determination of apolipoprotein B by kinetic (rate) nephelometry. J Lipid Res 1982;23: 893–902.
25 Thompson GR. Plasma exchange for hypercholesterolaemia: a therapeutic mode and investigative tool. Plasma Ther 1980; 1:5–15.
26 Armstrong VW, Eisenhauer T, Noll D, Wieland H, Scheler F, Seidel D. Extracorporeal plasma therapy: the HELP system for the treatment of severe hyper-β-lipoproteinemia. In: Widhalm K, Naito HK, eds. Recent Aspects of Diagnosis and Treatment of Lipoprotein Disorders. New York: Alan R. Liss, 1988:327–35.
27 Kesaniemi YA, Vega GL, Grundy SM. Kinetics of apolipoprotein B in normal and hyperlipidemic man: review of current data. In: Berman M, Grundy SM, Howard BV, eds. Lipoprotein Kinetics and Modeling. New York: Academic Press 1982: 181–205.
28 Thompson GR, Myant NB. Low density lipoprotein turnover in familial hypercholesterolaemia after plasma exchange. Atherosclerosis 1976;23:371–7.
29 Thompson GR, Spinks T, Ranicar A, Myant NB. Non-steady-state studies of low-density lipoprotein turnover in familiar hypercholesterolemia. Clin Sci Mol Med 1977;52:361–9.
30 Soutar AK, Myant NB, Thompson GR. Metabolism of apolipoprotein B containing lipoproteins in familial hypercholesterolaemia. Effects of plasma exchange. Atherosclerosis 1979;32: 315–27.
31 Havekes L, Vermeer BJ, Brugman T, Emeis J. Binding of Lp(a) to the low density lipoprotein receptor of human fibroblasts. FEBS Letters 1981;132:169–73.
32 Floren CH, Albers JJ, Bierman EL. Uptake of Lp(a) lipoprotein by cultured fibroblasts. Biochem Biophys Res Commun 1981;102:636–9.
33 Krempler F, Kostner GM, Roscher A, Haslauer F, Bolzano K, Sandhofers F. Studies on the role of specific cell surface receptors in the removal of lipoprotein(a) in man. J Clin Invest 1983;1:1431–41.
34 Martmann-Moe H, Berg K. Lp(a) lipoprotein enters cultured fibroblasts independently of the plasma membrane low density lipoprotein receptor. Clin Genet 1983;20:352–62.