Non-pharmacological procedures: treatment of severe hypercholesterolaemia in patients with coronary heart disease by means of heparin-induced extracorporeal low-density lipoprotein plasmapheresis

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Introduction

Diseases resulting from premature atherosclerosis are the most common cause, not only of death, but also of early retirement (Castelli *et al.*, 1990; Cremer and Muche, 1990). The results of many studies have shown that there is a large number of factors involved in atherogenesis. Disturbances in lipid metabolism (hyperbetalipoproteinaemia, hypoalphalipoproteinaemia, accumulation of chylomicron and very low-density lipoprotein (VLDL) remnants), structural abnormalities of lipoproteins, and family history of myocardial infar-

cation (MI) are the most important risk factors. Hypertension, smoking, elevated blood glucose and overweight also have an impact on early cardiovascular events. More recently, lipoprotein(a) (Lp(a)), fibrinogen and the biological modification of lipoproteins have been added to the list of risk factors for atherosclerosis (Smith, 1986, 1990; Kienast *et al.*, 1990; Koenig and Ernst, 1992; Seidel *et al.*, 1992).

In many patients suffering from coronary heart disease (CHD), low-density lipoproteins (LDL), Lp(a) and fibrinogen are elevated at the same time and may potentiate the cardiovascular risk derived from each factor alone. Most forms of hypercholesterolaemia result from a defect in the removal of LDL from plasma by the liver and the LDL receptor is now recognized as the crucial element in the control of LDL-cholesterol (LDL-C) homeostasis (Seidel *et al.*, 1985; Brown and Goldstein, 1986). If the physiological clearing mechanisms for LDL are insufficient, diet and drug therapy alone are often ineffective. This also holds true for Lp(a) and fibrinogen, neither of which at present can be adequately lowered by diet or drugs.

In humans, plasma LDL-C levels below 110 mg/dl seem to be necessary to inhibit the development of atherosclerosis or to induce the regression of vessel-wall lesions (Cremer *et al.*, 1991). This has been impressively demonstrated in six different secondary intervention studies: the Lifestyle Heart Study (Ornish *et al.*, 1990), the Report of the Program on the Surgical Control of the Hyperlipidaemias (POSCH study) (Buchwald *et al.*, 1990), the Femoral Atherosclerosis Treatment Study (FATS) (Brown *et al.*, 1990), the Cholesterol-Lowering Atherosclerosis Study (CLAS) (Blankenhorn *et al.*, 1987), the Mevinolin Atherosclerosis Research Study (MARS) (Blankenhorn, D.H. *et al.* and the MARS Research Group, personal communication, 1992), and the Heparin-Induced Extracorporeal LDL Precipication (H.E.L.P.), multicentre study (Schuff-Werner *et al.*, 1989, 1993; Hennerici *et al.*, 1991). Although the therapeutic approach and strategy were different in these studies, the outcome was unique and promising. Lowering of LDL-C by 35–50% was followed by a two-fold increase in the progression : regression ratio when controls were compared with treated patients.

The cornerstone of strategies to reduce the risk of CHD in the population is undoubtedly diet. With the advent of the 3-hydroxy-3-methylglutaryl–coenzyme A (HMG–CoA) reductase inhibitors, a new class of powerful lipid-lowering drugs has been introduced with great potential in the treatment of hypercholesterolaemia. The use of these drugs is now increasing, and long-term safety will be of profound importance for their general application in the treatment of atherosclerotic disease. More radical measures such as partial ileal bypass (Buchwald, 1964), portocaval shunt (Starzl *et al.*, 1983), liver transplantation (Starzl *et al.*, 1984), plasma exchange (De Gennes *et al.*, 1967; Thompson *et al.*, 1975) and LDL apheresis (Lupien *et al.*, 1976) have also been introduced for the treatment of severe hypercholesterolaemia.

Plasma exchange has proven to be particularly successful in the management of severe hypercholesterolaemia such as homozygous familial hypercholesterolaemia (FH) (De Gennes *et al.*, 1967; Thompson *et al.*, 1975). Since this therapy requires substitution of plasma fractions with its inherent danger, several LDL apheresis procedures with varying degrees of selectivity and efficiency have subsequently been developed, some of which are at present being evaluated in clinical trials.

While the use of such therapies for the primary prevention of CHD will largely be restricted to the most severe forms of hypercholesterolaemia (Greten *et al.*, 1992), in secondary prevention the combination of diet and drugs together with plasmapheresis seems to be an attractive therapeutic possibility, if diet and drug therapy alone is not sufficient to achieve the therapeutic goal of LDL-C <110 mg/dl. The combination of plasma LDL apheresis together with diet and drugs now allows a maximal lowering of LDL-C of up to 80%. This also holds true for patients who, only a few years ago, were classified as resistant to the treatment of hypercholesterolaemia. Besides LDL, some apheresis procedures also eliminate other risk factors for CHD which are of clinical importance, such as Lp(a) and fibrinogen. The latter will greatly improve the haemorheological status of the patients.

Low-density lipoprotein apheresis procedures

Several systems have been developed for the extracorporeal elimination of LDL-cholesterol from plasma. These procedures are collectively referred to as LDL apheresis. Today, LDL apheresis has largely replaced plasma-exchange therapy as introduced by De Gennes (1967) and later also by Thompson *et al.* (1975). Now, with the experience gathered over the course of several years of clinical application, the efficiency, specificity and safety of the different LDL apheresis methods can be compared. Besides the marked reduction in LDL-C concentrations by all techniques, it has become apparent that at least one of the procedures (the H.E.L.P. system) results in an equally significant change in haemorheology.

Three methods of LDL apheresis have been clinically established and are now used for the treatment of severe hypercholesterolaemia:

- various LDL immunoadsorption techniques, using immobilized monoclonal or polyclonal antibodies to apolipoprotein apoB-100 (Stoffel and Demant, 1981; Riesen *et al.*, 1986)
- LDL binding by dextrane sulphate attached to cellulose (Yokoyama *et al.*, 1985)
- heparin-induced extracorporeal LDL precipitation (Seidel and Wieland, 1982; Eisenhauer *et al.*, 1987).

Plasma membrane filtration has also been proposed, but this retains, apart from LDL, other macromolecules such as high-density lipoproteins (HDL), immunglobulins and albumin and therefore cannot be considered as being specific. This technique closely resembles plasma exchange, with its disadvantages for long-term therapy.

The heparin-induced extracorporeal LDL plasmapheresis (H.E.L.P.. system) has been widely used. Its efficiency and safety, alone and in combination with HMG CoA reductase inhibitors, have been investigated in great detail. Therefore this review will focus on the H.E.L.P. system as a new therapeutic tool to lower LDL, Lp(a) and fibrinogen, and at the same time, to improve haemorheology and to achieve regression of coronary sclerosis in patients who were otherwise refractory to the treatment of severe hypercholesterolaemia.

Heparin-induced extracorporeal low-density lipoprotein plasmapheresis

This technique operates by an increase in the positive charges on LDL and Lp(a) particles at low pH, allowing them to form specifically a network with heparin and fibrinogen in the absence of divalent cations (Seidel and Wieland, 1982; Armstrong, 1987; Seidel, 1990). Only a limited number of other heparin-binding plasma proteins are coprecipitated by heparin at low pH. Other proteins, such as apoA-I, apoA-II, albumin or immunoglobulins, do not significantly bind to heparin at low pH and are not precipitated in the system (Eisenhauer *et al.*, 1987; Armstrong, 1987). Complement activation takes place in all extracorporeal therapy systems. However, as a specific feature of the H.E.L.P. system, activated complement C3 and C4 as well as the terminal complement complex are largely adsorbed to the precipitation filter, resulting in plasma concentrations below those measured before apheresis (Würzner *et al.*, 1991). Leucocytopaenia, a hallmark of complement activation, has not been observed under H.E.L.P. therapy.

The H.E.L.P. system (manufactured by B. Braun Melsungen, Germany) has the following unique features.

- It removes LDL, Lp(a) and fibrinogen with high efficiency.
- It does not remove HDL.
- It does not alter or modify plasma lipoproteins.
- It does not change plasma concentrations of cell mediators.
- It avoids the use of compounds with immunogenic or immunostimulatory activity.
- It uses only disposable material and avoids regeneration of any of the used elements.
- It is a technically safe and well-standardized procedure.
- In both short-term and long-term treatment, tolerance and benefit are excellent.
- Its clinical utility has been established by the outcome of controlled clinical trials.

The major steps of the H.E.L.P. system to remove the atherogenic compounds are illustrated in the flow sheet (see Fig. 71.1).

In the first step, plasma is obtained by filtration of whole blood through a plasma separator. This is then mixed continuously with a 0.3 M acetate buffer, pH 4.85, containing 100 IU heparin/ml. The sudden precipitation occurs at a pH of 5.12, and the suspension is circulated through a 0.4 M polycarbonate filter to remove the precipitated LDL, Lp(a) and fibrinogen. Excess heparin is absorbed by passage through an anion-exchange column which binds only heparin at the given pH. The plasma–buffer mixture is finally subjected to a bicarbonate dialysis and ultrafiltration to remove excess fluid and restore the physiological pH, before the plasma is mixed with the blood cells and returned to the patient. All filters and tubing required for the treatment are sterile, disposable and intended for a single use only. This

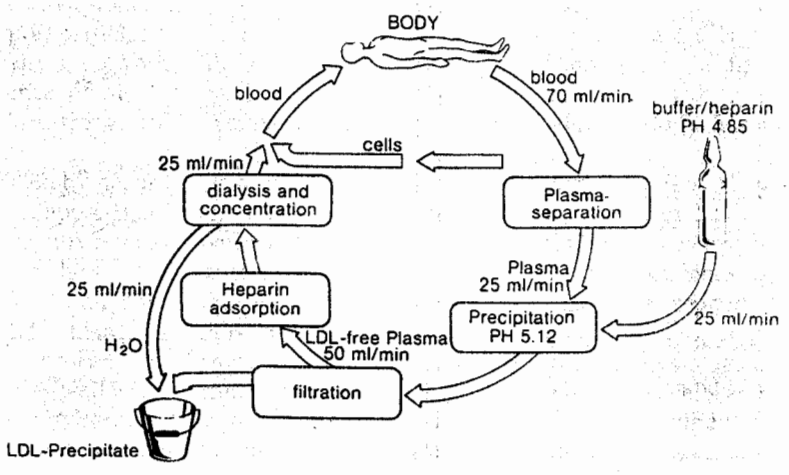

Fig. 71.1 Flow sheet of the H.E.L.P. procedure.

makes it easy and reliable to work with the system and guarantees a steady quality for each treatment, independent of the clinic performing the procedure. Safety is assured by a visual display and two microprocessors operating in parallel (Fig. 71.2). Owing to the excellent tolerance of the procedure patients can leave the hospital shortly after the end of the treatment session.

CLINICAL EXPERIENCE WITH THE H.E.L.P. SYSTEM

Clinical experience with the H.E.L.P. system goes back to 1985. Up to 1992, approximately 320 patients were treated in over 40 000 single treatments. Some patients have been treated for more than five years. Currently, the system operates in approximately 100 centres in Germany, Italy, the USA, Austria and Ireland. The efficiency of the system is 100% for the elimination of LDL, Lp(a) and fibrinogen. Each single session (lasting 1.5–2 h) treats 2.8–3 l of plasma, causing a reduction of approximately 50% of these three compounds in plasma of the treated patients.

The rates of return to preapheresis concentrations for LDL differ between normocholesterolaemics and heterozygous as well as homozygous FH patients, while they are almost identical for Lp(a) (Armstrong *et al.*, 1989; Thiery *et al.*, 1990). Normocholesterolaemics return rather quickly towards the steady-state pretreatment levels. Heterozygous FH patients display a rate of return intermediate between normocholesterolaemics and a homozygous FH patient, the latter being slowest in her rate of return to pretreatment LDL concentrations. At biweekly treatment intervals the pretreatment values usually reach a new steady state after four to eight treatments.

Long-term effects of the H.E.L.P. treatment, based on interval values between two treatments ((concentration after H.E.L.P. + concentration before H.E.L.P.)/2) and expressed as a percentage of concentrations at the start of treatment are shown in Table 71.1.

The H.E.L.P. treatment also significantly improves plasma viscosity (−15%), erythrocyte aggregation (−50%) and erythrocyte filtration (+15%), which is followed by an acute (20–30%) increase in the oxygen tension in muscle tissue (Schuff-Werner *et al.*, 1989; Kleophas *et al.*, 1990). The changes in plasma viscosity are due to the reduction in both LDL and fibrinogen. The change in erythrocyte aggregation is primarily due to fibrinogen reduction. Changes in erythrocyte filtrability correlate with an improvement in the cholesterol : phospholipid ratio of cell membranes (Schuff-Werner *et al.*, 1989). It is conceivable to associate the rheological findings with the impressive relief from angina, together with the improvement in exercise electrocardiogram (ECG) and in physical capacity observed in most (over 90%) of the patients shortly (2–3 months) after start of therapy (Schuff-Werner *et al.*, 1989; Kleophas *et al.*, 1990; Seidel, 1990).

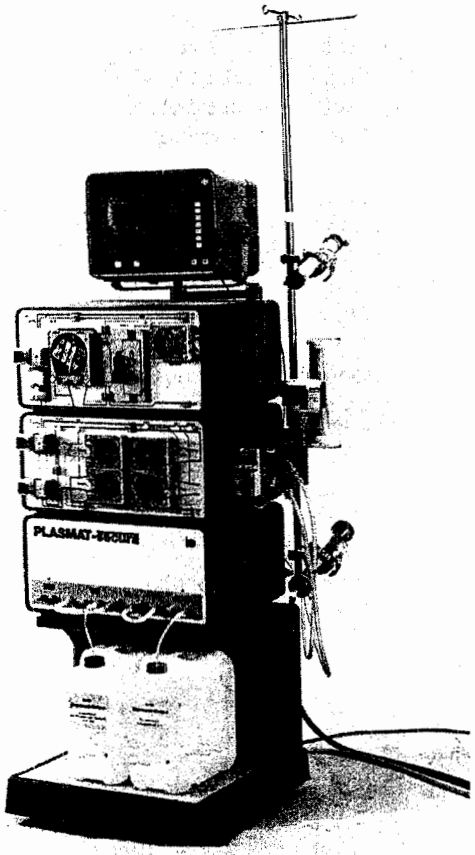

Fig. 71.2 HD Secura H.E.L.P. system (manufactured by B. Braun Melsungen, Germany).

CLINICAL UTILITY OF THE H.E.L.P. TREATMENT

The first coronary angiographies two years after H.E.L.P. treatment in over 50 patients (Schuff-Werner *et al.*, 1993) lend support to the hope that regression of CHD is possible in humans. Angiographies obtained before and after two years of regular treatment could be evaluated blindly, using the Cardiovascular Angiogra-

Table 71.1 Long-term effects of H.E.L.P. treatment

Factor	Mean interval values of ~6000 treatments (% ± SEM)
LDL-C	−51 ± 14
Lp(a)	−45 ± 5
Fibrinogen	−46 ± 15
ApoB-100	−45 ± 10
HDL-C	+12 ± 2
ApoA-I	+9 ± 2

phy Analysis System (CAAS) (Reiber, 1988). The mean degree of stenosis of all segments decreased from 32.5 to 30.6. A regression of >8% the size of the lesions was observed in 27% of the segments, whereas only 15% of the segments showed progression. It is important to note that higher degree stenosis (>30%) showed more impressive size reductions after two years than did lower degree stenosis. The mean cross-sectional area of the lesions (>30%) was increased by 16%. These findings are in agreement with earlier reports by Hombach *et al.* (1986), Brensike *et al.* (1984), Brown *et al.* (1990), Kane *et al.* (1990) and Gohlke (1991) obtained with LDL immunoadsorption.

The results clearly demonstrate that regular treatment with H.E.L.P. favourably influences the cause of progressive coronary artery disease. The natural history of coronary lesions in patients with severe hypercholesterolaemia is known from control groups of several prospective studies. Progression of coronary lesions occurs three to seven times more frequently than regression within an observation period of two to three years, and only moderate lowering of plasma LDL-C cannot reverse the progression of the disease in CHD patients.

Another impressive demonstration of the clinical utility of H.E.L.P. LDL apheresis in the treatment of CHD is derived from 180 patients who were receiving treatment for more than four years (Fig. 71.3). In this group of patients the incidence of MI recorded from history over a period of 10 years prior to the H.E.L.P. treatment indicated an average MI incidence of 4.5/year. During the two years prior to the H.E.L.P. treatment 15 incidences occurred. Immediately after the H.E.L.P. treatment the high incidence of 15 per two years decreased to three per two years and only one MI incidence was recorded two years after the start of the H.E.L.P. therapy for the entire group. Of the total group of patients ($n = 315$) so far treated with the H.E.L.P. system 15 suffered from a non-treatment-related cardiac death during a cumulative treatment time of 9301 months. This can be calculated as one fatal cardiac event in 52 years of H.E.L.P. treatment, an impressively low death rate for the high-risk group of patients treated with the system.

EXPERIENCE WITH COMBINED H.E.L.P. AND 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR THERAPY

HMG CoA reductase inhibitors were not available when the H.E.L.P. multicentre study started. As these compounds are now on the market, the effects of combined therapy, using lovastatin, simvastatin or pravastatin together with LDL apheresis, have since been investigated.

In cases with plasma cholesterol levels exceeding 300 mg/dl, the use of specific diets and drugs may not be sufficient if the aim is to achieve LDL concentrations <110 mg/dl and/or the regression of CHD as a means of secondary intervention.

Therefore, the efficacy of a combined therapy was investigated, using HMG CoA reductase inhibitors (Lovastatin®, Simvastatin® and Pravastatin®) together with H.E.L.P. apheresis, and approximately 80 patients with severe FH were treated on a long-term basis. These compounds significantly decrease the rate of return after H.E.L.P. apheresis in both heterozygous and homozygous FH patients by 20–30% (Armstrong *et al.*, 1989; Seidel, 1990; Thiery *et al.*, 1990). When the two treatments are combined, a reduction in the interval LDL-C level of 70% may be achieved, while Lp(a) and fibrinogen are not further affected (over the effect by the H.E.L.P. treatment alone) (Table 71.2). In the combined form, therapy intervals between two H.E.L.P. treatments may, in many cases, be extended from 7 to 14 days, depending on the rate of synthesis for LDL or the severity of CHD.

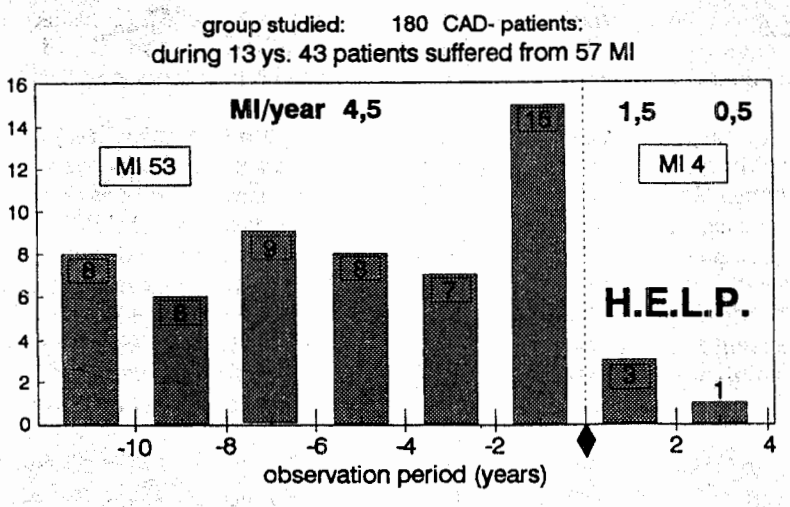

Fig. 71.3 Incidence of MI before and under long-term H.E.L.P. treatment. Observation period: 13 years.

Table 71.2 Long-term effects of H.E.L.P. and HMG CoA reductase inhibitor treatment

	Mean interval values of ~1400 treatments	
Factor	HMG CoA reductase inhibitor (% ± SEM)	H.E.L.P. + HMG CoA inhibitor (% ± SEM)
LDL-C	−38 ± 12	−69 ± 12
HDL-C	+10 ± 9	+14 ± 6
Apo B	−30 ± 9	−53 ± 8
Apo A-I	+13 ± 4	+12 ± 9
Lp(a)	No change	−43 ± 7
Fibrinogen	No change	−44 ± 10

TREATMENT TOLERANCE AND SAFETY OF H.E.L.P.

Overall treatment tolerance has been very good and no major complications have been observed after 40 000 treatments in approximately 320 patients. The treatment effects have been maintained on long-term treatment for over six years. At the end of the H.E.L.P. therapy, plasma concentrations of proteins that are not selectively precipitated by heparin at low pH were generally in the range of 80–90% of the initial values and returned to their original level no later than 24 hours after the end of the treatment (Eisenhauer *et al.*, 1987; Seidel, 1990; Seidel *et al.*, 1991). No substitution of any kind has been necessary in seven years of clinical experience. In contrast to some other LDL apheresis systems, the H.E.L.P. procedure alters neither the physicochemical characteristics of LDL nor the ligand quality of LDL for lipoprotein receptors (Schultis *et al.*, 1990). Special attention has been focused on the effect of H.E.L.P. on haemostasis. All post-treatment controls were typical for extracorporeal procedures, and no critical bleeding complications have been observed. Complement activation is found in all extracorporeal procedures. However, as a specific feature of the H.E.L.P. system, activated complement C3 and C4 and the terminal complement complex are largely adsorbed to the filter system of H.E.L.P., resulting in plasma concentrations below those measured before LDL apheresis. C5a is not retained in the filter system but plasma levels at the end of the treatment are within the normal range, and leucocytopaenia, a hallmark of complement activation, has never been observed under H.E.L.P. treatment (Würzner *et al.*, 1991). Plasma electrolytes, hormones, vitamins, enzymes and immunoglobulin concentrations, as well as haematological parameters, remained virtually unchanged at the end of each treatment and on long-term application (Seidel, 1990; Thiery *et al.*, 1990; Seidel *et al.*, 1991) (see Table 71.3).

Case reports

CASE I

A typical follow-up kinetic for LDL and Lp(a) under H.E.L.P. treatment of a patient with severe progressive coronary heart disease is shown in Fig 71.4.

At the start of therapy the 33-year-old MI patient had a coronary bypass and percutaneous transluminal coronary angioplasty (PTCA) showed LDL-C levels of 350 mg/dl and a marked Lp(a) elevation of 165 mg/dl. LDL-C was lowered with a HMG CoA reductase inhibitor (simvastatin) by about 48% to 170 mg/dl, but no effect on Lp(a) levels was observed. In combination with regular H.E.L.P. treatment the LDL concentration was maintained at an interval value of 110 mg/dl. In addition, H.E.L.P. treatment resulted in a marked decrease (−70%) in post-apheresis Lp(a) concentrations. The interval Lp(a) levels were maintained around 90 mg/dl. Fibrinogen was lowered from a baseline value of 317 mg/dl to a H.E.L.P. interval value of 177 mg/dl, which is a 44% reduction. A control angiography after two years revealed that the combined treatment was able to stop the highly progressive CHD, which was developing in the patient before treatment. The clinical situation has also improved considerably.

CASE II

Experience with H.E.L.P. treatment in a homozygous form of FH is show in Fig. 71.5.

Early death from the cardiac consequences of premature coronary sclerosis and aortic stenosis is the usual outcome of homozygous FH (Goldstein and Brown, 1983). Inherited as an autosomal dominant defect of the LDL receptor gene, this disease is characterized by very high plasma LDL–C concentrations (between 200 and 1000 mg/dl) and the development of severe cutaneous and tendon xanthomata in childhood. All conventional lipid-lowering treatments with diet and medication are completely insufficient.

Since 1985 the author has been treating a FH patient, born in 1979, with the H.E.L.P. apheresis procedure (Thiery *et al.*, 1990). LDL-C concentrations before the start of treatment exceeded 800 mg/dl. The follow-up of LDL concentrations under H.E.L.P. treatment alone and in combination with lovastatin and regular cholestyramine is shown in Fig. 71.5. The girl was treated for two years with weekly H.E.L.P. apheresis. Under this procedure the LDL-C interval levels were maintained below 280 mg/dl. At this time a rapid regression of multiple xanthomata could be observed. With additional medication of lovastatin and cholestyramine a further LDL decrease

Table 71.3. H.E.L.P. therapy in combination with HMG CoA reductase inhibitor: laboratory data

Parameter	Units	Baseline (mean ± SEM)	24 months simvastin +H.E.L.P. treatment (mean ± SEM)
Substrates:			
Sodium	mmol/l	140.0 ± 0.7	141.0 ± 0.8
Potassium	mmol/l	3.9 ± 0.12	4.0 ± 0.05
Calcium	mg/dl	9.2 ± 0.11	8.9 ± 0.1
Phosphate	mg/dl	3.7 ± 0.16	3.3 ± 0.03
Iron	µg/dl	88.2 ± 9.3	95.5 ± 3.9
Creatinine	mg/dl	0.85 ±0.04	0.9 ± 0.02
Blood urea nitrogen	mg/dl	15.2 ± 1.7	14.5 ± 0.4
Uric acid	mg/dl	5.3 ± 0.4	5.3 ± 0.4
Glucose	mg/dl	94.0 ± 0.9	100.0 ± 6.4
Total b/	mg/dl	0.43 ± 0.03	0.56 ± 0.4
Total p/	g/dl	7.0 ± 0.1	6.9 ± 0.1
Albumin	%	61.6 ± 1.73	61.4 ± 0.42
α_1-Protein	%	3.6 ± 0.3	3.6 ± 0.1
α-Protein	%	8.0 ± 0.42	8.3 ± 0.14
β_2-Protein	%	13.0 ± 0.56	12.0 ± 0.03
γ-Protein	%	13.7 ± 0.99	14.8 ± 0.14
Enzymes:			
Alanine amino transferase	U/l	10.0 ± 0.4	13.5 ± 0.4
Aspartate aminotransferase	U/l	11.0 ± 2.0	19.0 ± 1.0
Glutaryl transpeptidase	U/l	21.0 ± 5.8	25.0 ± 2.1
Creatine kinase	U/l	45.0 ± 7.0	45.0 ± 2.0
Lactate dehydrogenase	U/l	143.0 ± 10.8	151.0 ± 4.6
Amylase	U/l	16.0 ± 2.7	16.0 ± 0.3
Cholinesterase	U/l	5151.0 ± 525.0	5455.0 ± 530.0
Alkaline phosphate	U/l	101.0 ± 6.6	110.0 ± 2.8
Haematological indices:			
Haemoglobin	g/dl	14.0 ± 0.44	14.3 ± 0.07
Haematocrit	%	41.8 ± 1.1	42.0 ± 0.73
Erythrocytes	10^6/µl	4.4 ± 0.14	4.6 ± 0.1
Thrombocytes	10^3/µl	226.0 ± 10.2	220.0 ± 9.5
Leucocytes	10^3/µl	5.18 ± 0.39	5.22 ± 0.48
Lymphocytes	%	37.4 ± 2.76	33.3 ± 2.1
Monocytes	%	7.2 ± 1.02	6.2 ± 2.45
Neutrophils	%	51.3 ± 3.16	57.4 ± 3.12
Eosinophils	%	2.6 ± 0.43	1.8 ± 0.61
Basophils	%	0.7 ± 0.18	0.7 ± 0.1
Haemostasis:			
Quick-test prothrombin time	%	98.0 ± 1.25	99.0 ± 0.91
Thrombin time	s	14.0 ± 0.12	14.0 ± 0.21
Endocrinological indices:			
Cortisol	µ/dl	12.6 ± 1.05	13.3 ± 1.15
Testosterone	µ/dl	6.7 ± 1.07	6.4 ± 0.26
Adrenocorticotropic hormone	µ/dl	40.3 ± 3.78	40.4 ± 6.18
Luteinizing hormone[a]	ng/ml	15.9 ± 8.36	11.1 ± 5.91
Follicle-stimulating hormone	ng/ml	16.0 ± 0.22	28.0 ± 10.3
T3	ng/ml	133.5 ± 7.35	123.5 ± 12.4
T4	µg/dl	7.0 ± 0.61	7.3 ± 0.1
FT4	µg/dl	7.5 ± 0.62	7.5 ± 0.6
FT3	ng/ml	142.5 ± 7.64	137.5 ± 6.01

[a]Males or premenopausal females.

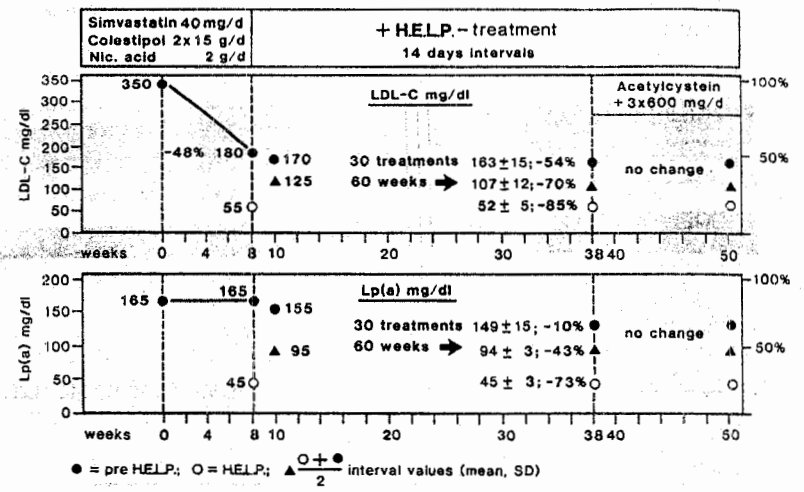

Fig. 71.4 Maximal treatment of FH and elevated plasma Lp(a) concentrations. Patient N.J., 33-year-old male. Baseline LDL-C, 350 mg/dl; Lp(a), 165 mg/dl; ACVB, PTCA. Well-maintained PTCA: results after one year of treatment and no further progression of CHD.

to 180 mg/dl was achieved. The treated plasma volume has recently been enhanced from 1.5 to 2.5 l. This has resulted in a mean LDL-C level of 160 mg/dl, which is equivalent to a decrease of 80% compared with pre-treatment values. The therapy is tolerated excellently. The girl is well and shows normal growth and development. No signs of cardiovascular symptoms have been noted.

H.E.L.P. treatment in heart-transplant patients with severe hypercholesterolaemia

The goal of this ongoing trial is to decrease recurrent CHD of heart grafts. In this study the patients will be followed for four years. LDL-C concentrations in all

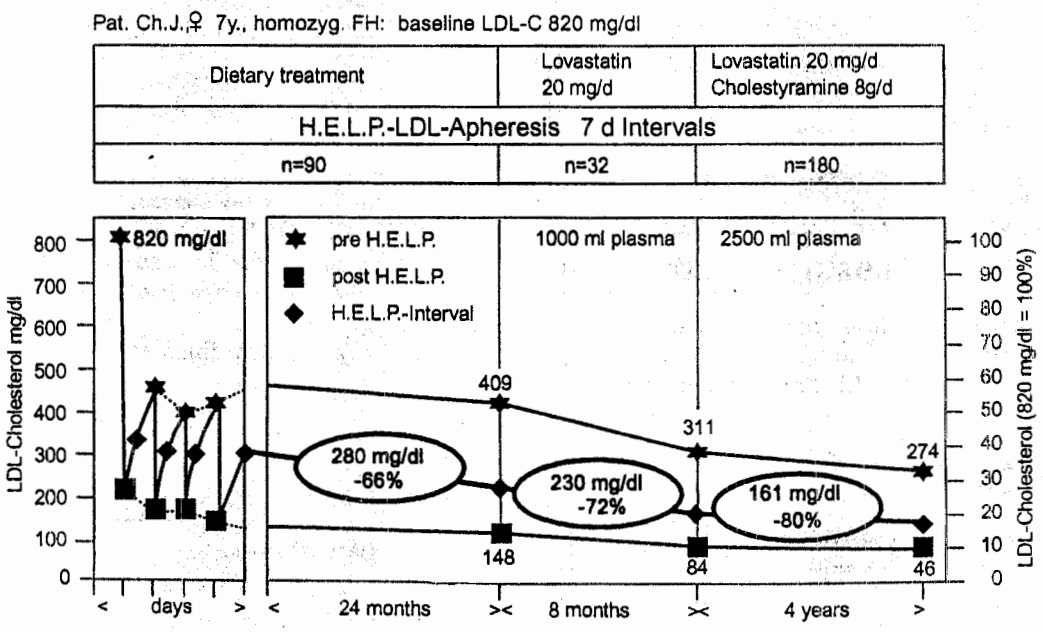

Fig. 71.5 Maximal treatment of homozygous FH: follow-up of LDL-C. Patent Ch.J., 7-year-old female, homozygous FH. Baseline LDL-C, 820 mg/dl.

patients are maintained at a level below 120 mg/dl. Treatment was started from a baseline LDL-C concentration >280 mg/dl with simvastatin, which resulted in a 40% reduction of LDL-C, but this still exceeded 170 mg/dl LDL. With the combination of simvastatin and H.E.L.P. treatment a LDL-C concentration <120 mg/dl was achieved. As in other H.E.L.P. patients overall treatment tolerance in this group (n = 5) has been very good and no major complications have been observed for the first six months of therapy. Special attention has been given to the tolerance and pharmacokinetics of both simvastatin and cyclosporine A. No signs of myopathy have been observed. No changes were observed in cell mediators such as interleukin II receptor, interleukin VI receptor, interferon-gamma and tumour necrosis factor before and after H.E.L.P. treatment.

From our first clinical experience in heart-transplant patients with severe hypercholesterolaemia the additional therapy with H.E.L.P. LDL apheresis may be not only useful, but necessary to achieve long-lasting benefit from the transplantation. Annual examination by angiograms should provide a rationale for the drastic LDL-lowering therapy in the prevention of graft atherosclerosis in heart-transplant patients.

Comparison of techniques to lower low-density lipoproteins by apheresis

Three methods for the selective removal of LDL from plasma have been established and are now used for the treatment of severely hypercholesterolaemic patients:

- LDL immunoadsorption, using immobilized anti-apoB antibodies for LDL binding (Stoffel and Demant, 1981; Riesen *et al.*, 1986)
- LDL binding to dextran sulphate cellulose (DSC) (Yokoyama *et al.*, 1985) and
- heparin-induced extracorporeal LDL precipitation (H.E.L.P.) (Seidel and Wieland, 1982; Eisenhauer *et al.*, 1987).

In two recent reviews (Keller, 1991; Demant and Seidel, 1992) the different procedures were compared with regard to their efficiency in lowering LDL concentrations and safety.

Immunoadsorption, heparin precipitation and dextran sulphate binding all achieve an approximately 60% decrease of LDL plasma concentrations in the course of a single LDL apheresis session. The reduction in HDL levels, albumin and immunoglobulins is usually less than 20%, with no significant difference between the three LDL apheresis methods. These apparent losses may to some extent be due to non-specific plasma dilution by the saline priming solution from the extracorporeal plasma circuit.

Double plasma filtration, although also effective in reducing LDL, is not selective. Total plasma protein loss (HDL, immunglobulins, α_2-macroglobulin and albumin) is significant and produces clinical problems. Concomitant albumin substitution is regularly required. Therefore, double plasma filtration occupies a position close to plasma exchange and should not be recommended for FH treatment.

Immunoadsorption and DSC apheresis are highly specific for apoB-containing lipoproteins, which include very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and Lp(a). It has recently been demonstrated that increased Lp(a) concentrations are significantly correlated with increased risk for CHD. Immunoadsorption, DSC LDL apheresis and H.E.L.P. LDL apheresis all eliminate Lp(a) to about the same extent as LDL. In contrast to immunoadsorption and DSC apheresis, H.E.L.P. LDL apheresis also eliminates fibrinogen. Parallel measurements of plasma viscosity and erythrocyte aggregation before and after H.E.L.P. LDL apheresis revealed a significant reduction of 15 and 50%, respectively (Schuff-Werner *et al.*, 1989). The muscle oxygen tension was found to be significantly higher directly after treatment, compared with pretreatment values, probably as a result of improved microcirculation under H.E.L.P. therapy (Schuff-Werner *et al.*, 1989; Kleophas *et al.*, 1990).

Results are available from multicentre studies using the H.E.L.P. and the DSC LDL apheresis as a means of drastic lipid-lowering therapy at this time (Hombach *et al.*, 1986; Gordon *et al.*, 1991; Seidel *et al.*, 1991; Tatami *et al.*, 1992; Schuff-Werner *et al.*, 1993). In the H.E.L.P. multicentre study 51 participants were examined by coronary angiography at the start and after two years of treatment. Evaluations of the angiographs with quantitative measurement of stenosis revealed a two-fold higher regression than progression rate of the coronary arteries in the patients under H.E.L.P. therapy (Seidel *et al.*, 1991; Schuff-Werner *et al.*, 1993). Another small study of seven patients with heterozygous FH produced evidence that H.E.L.P. LDL apheresis administered once a week for 7–24 months induced regression of carotid atherosclerotic plaques (Hennerici *et al.*, 1991). Plaques were evaluated by a three-dimensional reconstruction of ultrasound images. Out of 21 observed plaques, only one progressed, 12 did not change and eight regressed within 6–12 months.

Lechner and co-workers (Walzl *et al.*, 1993) were able to demonstrate the clinical benefit of early H.E.L.P. treatment in patients suffering from stroke or multi-infarct dementia. They concluded that only from the combination of an acute and efficient reduction of both LDL and fibrinogen could lasting clinical benefit be expected in their patients.

Data from one multicentre study using DSC LDL apheresis (Gordon *et al.*, 1991) are at present only available in preliminary form. In this study, 64 patients with FH (54 heterozygous and ten homozygous) were treated at 7–14 day intervals for 18 weeks. Baseline LDL-C concentrations were 243 mg/dl and 447 mg/dl, respectively. Time-averaged LDL-C levels on treatment were 139 mg/dl in heterozygotes and 210 mg/dl in homozygotes. HDL-C increased slightly but changes were not significant. Lp(a) levels were reduced markedly but long-term concentrations are not given.

The second DSC LDL Apheresis Multicenter Study (Tatami *et al.*, 1992) uses LDL apheresis combined with cholesterol-lowering drugs to treat homozygous or heterozygous FH. As a result by visual judgement or computer analysis, the coronary angiograms revealed a regression rate of approximately 38%, no change in 49% and progression in 14%, indicating an encouraging result of aggressive cholesterol-lowering therapy in coronary atherosclerosis of FH patients.

LDL immunoadsorption, DSC LDL apheresis and H.E.L.P. LDL apheresis are all safe and equally potent methods of extracorporeal LDL elimination. Lp(a) can also specifically be removed from plasma by these procedures. In addition, H.E.L.P. LDL apheresis selectively reduces plasma fibrinogen, which seems to have a beneficial effect on the microcirculation. Long-term observations show that besides the marked reduction in LDL-C some increase in HDL-C occurs, which may add to the antiatherogenic effect of LDL apheresis treatment. The major advantage of LDL apheresis over plasma exchange or filtration techniques is that during each treatment LDL-C is removed with comparable efficiency and may be applied more frequently, thus leading to much more efficient LDL lowering over time. No major effect on other essential plasma proteins such as albumin, α_2 macroglobulin, immunoglobulins or HDL is seen in LDL apheresis, in contrast to the filtration techniques. Therefore, changes in colloid-osmotic pressure with resulting oedema, increased susceptibility to infections and harmful effects on cholesterol metabolism are avoided. Adverse effects of the H.E.L.P. treatment were documented in less than 3% of all treatments and could be managed with no major problems.

Conclusions

LDL apheresis is the most potent technique for eliminating LDL and Lp(a) if the physiological clearing mechanisms are insufficient. In addition, the H.E.L.P. LDL apheresis system can very efficiently remove fibrinogen and therefore improve plasma viscosity and microcirculation.

Long-term observations show that besides the marked reduction in LDL-C there is a remarkable increase in HDL, which may add to the antiatherogenic effect of the extracorporeal procedures. For the future, new dimension may be provided for by the availability of safe and efficient apheresis techniques in the treatment of severe hypercholesterolaemia in patients with CHD.

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