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LDL – APHERESIS: REVIEW OF RECENT METHODS

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ABSTRACT

Hypercholesterolemia and the resulting atherosclerosis has been a major problem for the past few decades. Adequate control of serum cholesterol levels is generally achieved by dietary modifications and/or drug regimens. However some patients, particularly those with familial hypercholesterolemia, fail to respond. Additional treatment methods may be necessary to reduce LDL to safer levels in these individuals who are at high risk for atherosclerotic disease complications. Reduction of lipoproteins and Lp(a), of oxidation of LDL, improvement of the procoagulatory state and disturbed hemorheology associated with atherosclerosis, as well as the stabilization of plaques and the decrease of cytokines and adhesion molecules have been induced by apheresis and are thought to favorably influence regression of artherosclerosis.

Keywords: Apheresis, LDL, Cholesterol, Hypercholesterolemia, Dialysis

INTRODUCTION

LDL apheresis is an invasive procedure that selectively removes LDL cholesterol and other atherogenic lipoproteins from the blood via an extracorporeal circulation device. This new therapeutic tool may reduce the risk of progressive atherosclerotic disease in hypercholesterolemic patients who are resistant to diet and drugs. Lipids are transported in different lipoprotein fractions in blood. The protein part of the lipoprotein, apolipoprotein-B, and it's degradation products, are the atherogenic elements. The apolipoprotein-B (Apo B-100) is in highest concentration in LDL and is present in smaller amounts in very low density lipoprotein (VLDL). High-density cholesterol (HDL) levels lack the atherogenic apolipoprotein-B component and relate inversely to coronary artery disease risk (12) Figure 1. The low density lipoproteins are selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation (also referred to as HELP) or dextran sulfate adsorption. In immunoadsorption, polyclonal antihuman apoB antibodies from sheep selectively bind to and remove LDL. LDL and other particles containing apoB are precipitated by heparin at an acidic pH in the HELP procedure. Dextran sulfate adsorption removes LDL by binding the positively charged apoB to dextran sulfate particles bound to cellulose. The procedure takes 2-4 hours and must be repeated every several weeks to support LDL levels preventing accumulation and causing cardiovascular disease. It is an expensive procedure, limiting its use to severe cases of hyperlipidemia. LDL apheresis must be distinguished from plasma exchange (also referred to as plasmapheresis). In plasma exchange the plasma is collected during a pheresis procedure then discarded and replaced with crystalloids. In contrast, LDL apheresis is a selective procedure in which only pathogenic low density lipoproteins are removed.

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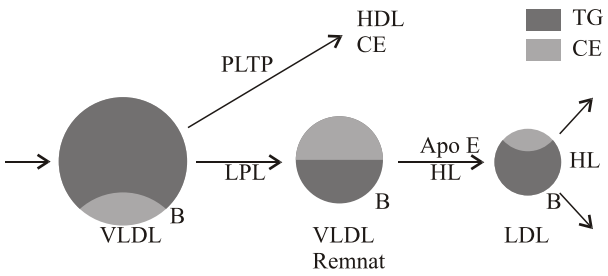

Fig. 1. The apolipoprotein B-100 cascade. VLDL is secreted from the liver with one apo B on the surface and triglyceride and cholesteryl ester in the core. Core triglyceride is hydrolyzed by lipoprotein lipase and becomes a remnant lipoprotein that is recognized by the liver. The remnant lipoprotein is further processed to form LDL, which has a cholesterol-rich core and an intact apo B on its surface. The LDL particle can be removed by peripheral or hepatic LDL receptors. As the VLDL core is hydrolyzed, the unesterified cholesterol and phospholipid are transferred to HDL by phospholipid transfer protein to become the cholesteryl ester of HDL. (CE-cholesteryl ester; HL- hepatic lipase; LPL-lipoprotein lipase; PLTP-phospholipid transfer protein; TG-triglyceride). Picture from: METABOLISM II: Diagnosis and Treatment of Dyslipidemia-18, April 2005. John D. Brunzell, R. Alan Failor

The plasma is then returned to the patient. LDL apheresis works by leading venous blood through a collumn coated with antibodies to apolipoprotein B (the main protein of LDL particles), dextran sulphate or polyacrylate, or by precipitating LDL with heparin at low pH. In all cases (apart from polyacrylate absorption), plasma is separated from cells by a cell separator - Figure 2.

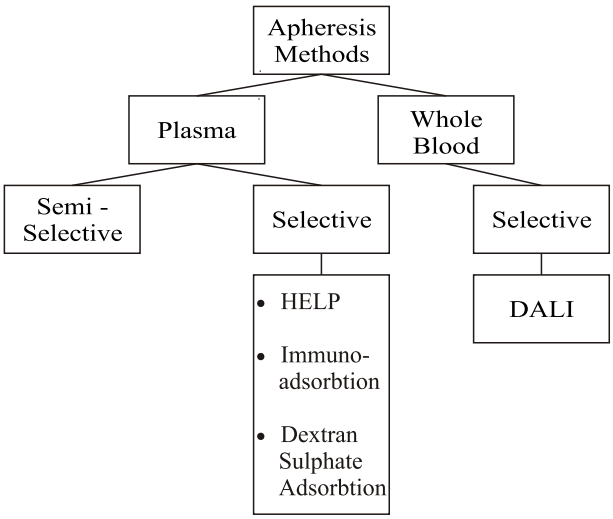

Fig. 2. Selective and semiselective apheresis methods

The most recently developed method enables lipoproteins to be adsorbed directly from whole blood, using polyacrylate columns. All 4 methods have proved to be similarly efficient when used weekly or biweekly to lower LDL cholesterol and Lp (a) without unduly reducing HDL cholesterol (14).

Familial hypercholesterolemia (FH) is a relatively common disorder caused by mutations of the LDL receptor gene that result in defects of LDL receptor function, or its complete absence, in hepatocytes and peripheral tissues (6). The LDL receptor is essential for the receptor-mediated endocytosis of plasma LDL and its delivery to lysosomes, where cholesterol is released for metabolic use. When LDL receptors are deficient, the rate of removal of LDL cholesterol from plasma declines, and the level of LDL cholesterol rises in inverse proportion to the receptor number. Cholesterol concentrations are elevated 3- to 6-fold above normal concentrations in homozygous patients. There are two forms of FH: heterozygous and homozygous. The heterozygous form is one of the most frequent metabolic disorders occurring in the general population (1:500), whereas the more severe homozygous form is much less common (1:1 million). Early diagnosis and treatment is essential for patients with FH in order to reduce the risk of developing cardiovascular diseases early in life, increase life expectancy and improve quality of life (3). In cases where dietary measures and drug therapy had failed, plasmapheresis was the initial physical method used in clinical practice to lower cholesterol levels (15,1). Plasmapheresis relies on membrane or centrifuge separation of plasma from whole blood. Albumin is then infused as a substitute solution for plasma. Plasmapheresis is simple and efficient but has two substantial disadvantages: the lack of selectivity of the process - immunoglobulins as well as high-density lipoprotein (HDL) are removed together with LDL and in addition to that is the high cost of albumin needed to substitute the plasma removed. Double-filtration plasmapheresis (DFPP) evolved from plasmapheresis by the addition of a secondary filter to the plasma circuit. The resultant filtrate is then reinfused. Although albumin is not required, the system is still nonselective and eliminates HDL and immunoglobulins from the circulation (10,17). The thermofiltration system is similar to DFPP; the secondary filter in the plasma circuit is warmed to about 40°C to prevent formation of a cryogel formation (as occurs in DFPP) which occludes the larger membrane pores of the secondary filter thereby decreasing the LDL-HDL selectivity of the filter (16). The more complicated procedure and more efficient is LDL apheresis. The dextran sulfate cellulose adsorption system uses columns containing dextran sulfate immobilized on cellulose beads to remove LDL from the plasma (17). Typically, there are 2 such columns in the plasma circuit, which are regenerated automatically during LDL apheresis (8). The system has a high selectivity for the removal of apolipoprotein B (apoB) - containing lipoproteins, removing LDL, very low-density lipoprotein, and lipoprotein(a), (see Figure 3).

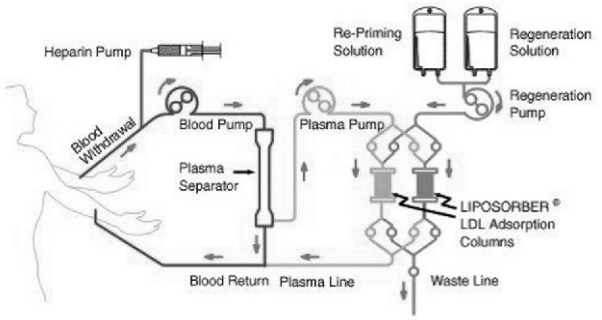

Fig. 3. Scheme of LDL apheresis unit

Binding of LDL appears to depend on electrostatic interaction between dextran sulfate and apoB and is inhibited by acetylation of LDL (11). Interestingly, dextran sulfate columns are able to remove LDL of patients with familial defective apoB with equal efficacy (9). Although some molecules with similar properties are adsorbed to the column, this is not associated with any adverse clinical consequences. The columns are discarded after each apheresis procedure, and this contributes to the high running costs of this system. The heparin extracorporeal LDL precipitation (HELP) system involves the removal of LDL-heparin complexes generated by the addition of heparin to plasma and their selective precipitation at a pH of 5.2. It is a system that can effectively remove LDL and fibrinogen. However, this system requires a filter, dialyzer, heparin, and buffer solution as well as a skilled operator to run it effectively (13).

The recently developed direct adsorption of lipoproteins (DALI) system uses columns of polyacrylate-coated polyacrylamide to remove apo B–containing lipoproteins from whole blood (5). This removal of lipoproteins from whole blood is based on an electrochemical interaction between the cationic groups of the lipoproteins and the column surface. Prolongation of the activated partial thromboplastin time has been noted after apheresis with this system. Because of this, less heparin is required to prevent extracorporeal clotting during apheresis in comparison with conventional systems (7).

The criteria for performing LDL apheresis are LDL cholesterol levels of 500 mg/dL or higher for homozygous FH patients, 300 mg/dL or higher for heterozygous FH patients in whom medical therapy has failed, and 200 mg/dL or higher for heterozygous FH patients with documented coronary disease and in whom medical therapy has failed (16).

Reduction of lipoproteins and Lp(a), of oxidation of LDL, improvement of disturbed vasomotion, the procoagulatory state and disturbed hemorheology associated with atherosclerosis, as well as the stabilization of plaques and the decrease of cytokines and adhesion molecules have been induced by apheresis and are thought to favorably influence regression of artherosclerosis (4).

CONCLUSION

Overall, these studies show that using LDL-apheresis can achieve a substantial lipid lowering effect in all or nearly all patients with severe hypercholesterolemia. The reduction is achieved regardless of prior response to dietary and/or drug interventions. A reduction in angina and stress test improvement was observed which did not correlate with the angiographic regression of the lesions. The rationale for this observation may be the improvement in blood flow due to changes in blood viscosity or blood vessel wall reactivity. Adequate control of serum cholesterol levels is generally achieved by dietary modifications and/or drug regimens, including HMG-CoA reductase inhibitors, bile acid binding resins, and nicotinic acid. However, a subset of patients, particularly those with familial hypercholesterolemia, fail to respond. Additional treatment methods may be necessary to reduce LDL to safer levels in these individuals who are at high risk for atherosclerotic disease complications (15). Figure 1. The apolipoprotein B-100 cascade. VLDL is secreted from the liver with one apo B on the surface and triglyceride and cholesteryl ester in the core. Core triglyceride is hydrolyzed by lipoprotein lipase and becomes a remnant lipoprotein that is recognized by the liver. The remnant lipoprotein is further processed to form LDL, which has a cholesterol-rich core and an intact apo B on its surface. The LDL particle can be removed by peripheral or hepatic LDL receptors. As the VLDL core is hydrolyzed, the unesterified cholesterol and phospholipid are transferred to HDL by phospholipid transfer protein to become the cholesteryl ester of HDL. (CE-cholesteryl ester; HL-hepatic lipase; LPL-lipoprotein lipase; PLTP-phospholipid transfer protein; TG-triglyceride). Picture from: METABOLISM II: Diagnosis and Treatment of Dyslipidemia-18, April 2005. John D. Brunzell, R. Alan Failor

REFERENCE

1. Apstein, C. S., D. B. Zilversmit, R. S. Lees , P. K. George. Effect of instensive plasmapheresis on the plasma cholesterol concentration with familial hypercholesterolemia. *Atherosclerosis*. 1978, **31**, 105-115.
2. Bosch, T., T. Wendler, H. Maschke. Modified DALI LDL-apheresis using trisodium citrate anticoagulation plus bicarbonate or lactate-buffered hemofiltration substitution fluids as primers. *Artif Organs*. 27, 2003, **6**, 55-64.
3. Carmen, M., C. Harstall. Low Density Lipoprotein Apheresis for the Treatment of Familial Hypercholesterolemia. *Alberta Heritage Foundation for Medical Research*, April 2004, IP-18 Information Paper.
4. Keller, C. Indication of Low-density Lipoprotein Apheresis in Severe Hypercholesterolemia and its Atherosclerotic Vascular Complications: Dextran Sulfate Cellulose Low-density Lipoprotein Apheresis. *Ther Apher Dial*. 7, 2003, **3**, 345-9.
5. Dräger, L. J., U. Julius, K. Kraenzle, J. Schaper, M. Toepfer, K. Zygan. DALI—the first human whole-blood low-density lipoprotein and lipoprotein (a) apheresis system in clinical use: procedure and clinical results. *Eur J Clin Invest*. 28, 1998, **12**, 994-1002.
6. Goldstein, J. L., H. H. Hobbs, M. S. Brown. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular *Bases of Inherited Disease*. Vol 2, 7th ed, New York, McGraw-Hill, 1995, 1981-2030.
7. Julius, U., G. Siegert, S. Gromeier. Intraindividual comparison of the impact of two selective apheresis methods (DALI and HELP) on the coagulation system. *Int J Artif Organs*. 23, 2000, **3**, 199-206.
8. Mabuchi, H., I. Michishita, M. Takeda, K. Fujita, J. Koizumi, R. Takeda, et al. A new low density lipoprotein apheresis system using two dextran sulfate cellulose columns in an automated column regenerating unit (LDL continuous apheresis). *Atherosclerosis*. 68, 1987, **1-2**, 19-25.
9. Maher, V. M., Y. Kitano, C. Neuwirth, J. J. Gallagher, G. R. Thompson, N. B. Myant. Effective reduction of plasma LDL levels by LDL apheresis in familial defective apolipoprotein B-100. *Atherosclerosis*. 95, 1992, **2-3**, 231-234.
10. Matsuda, Y., P. S. Malchesky, Y. Nose. Assessment of currently available low-density lipoprotein apheresis systems. *Artif Organs*. 18, 1994, **1**, 93-99.
11. Odaka, M., H. Kobayashi, K. Soeda, N. Murotani, Y. Saito, T. Nishide, et al. Adsorption of lipoprotein containing apolipoprotein-B through plasma separation for treatment of familial

hypercholesterolemia. *Int J Artif Organs*. 9, 1986, **5**, 343-348.
12. Shankar, R., E. J. Kiss. LDL APHERESIS: A New Treatment For Severe Dyslipidemia. *Transfusion Medicine Update* 1997, **5**.
13. Seidel, D., V. W. Armstrong, P. Schuff-Werner, T. Eisenhauer. Removal of low-density lipoproteins (LDL) and fibrinogen by precipitation with heparin at low pH: clinical application and experience. J *Clin Apheresis*. 4, 1988, **2-3**, 78-81.
14. Thompson, G., R. LDL Apheresis. *Atherosclerosis* 167, 2003, **1**, 1-13.
15. Thompson, G., R., R. Lowenthal, N. B. Myant. Plasma exchange in the management of homozygous familial hypercholesterolaemia. *Lancet*. 1, 1975, 1208-1211.
16. Vella, A., A. A. Pineda, T. O'Brien. Low-density lipoprotein apheresis for the treatment of refractory hyperlipidemia. *Mayo Clin Proc* 76, 2001, **10**, 1039-46.
17. Yokoyama, S., R. Hayashi, M. Satani, A. Yamamoto. Selective removal of low density lipoprotein by plasmapheresis in familial hypercholesterolemia. *Arteriosclerosis*. 5, 1985, **6**, 613-622.