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What's going on in LDL apheresis

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1. Introduction

Low-density lipoprotein (LDL) apheresis is a safe and very effective extracorporeal treatment for refractory hypercholesterolemia in order to prevent or to reduce coronary heart disease [1]. It is an invasive procedure that selectively removes LDL cholesterol and other lipoproteins from the plasma.

There are five different LDL apheresis techniques currently in use [2]:

(1) immunoadsorption (IMA), which consists of selective removal of LDL from plasma using polyclonal sheep anti-LDL antibodies;
(2) direct adsorption of lipoprotein from whole blood, hemoperfusion using non-hemolytic polyacrylate-coated polyacrilamide gel (DALI), with the advantage of a shorter procedure time;
(3) presently available, a new system of hemoperfusion which consists of an adsorption column system using multiporous cellulose beads as a carrier and dextran sulphate as ligand (DX-21);
(4) dextran sulphate-cellulose adsorption (DSA) using disposable dextran sulphate columns. This technique allows plasma to pass over the column and selectively bind very low-density lipoprotein (VLDL), LDL and lipoprotein A, commonly called Lp(a). Dextran sulphate has a structure similar to that of the LDL receptor in the human body and seems to act as a pseudo receptor for LDL;
(5) heparin extracorporeal LDL precipitation (HELP) system. This system uses heparin, a natural anticoagulant, as the medium to precipitate VLDL, LDL, and Lp(a) from extracorporeal plasma.

Only two techniques, HELP and DSA are approved by the US Food and Drug Administration (FDA) for clinical use.

2. LDL-apheresis beyond reduction of cholesterol

One of leading causative factors for early atherosclerosis and coronary heart disease is elevated lipid concentration, in particular, the abundance of LDL cholesterol in the blood, (exceeding limits of 100 mg/dL) that, by accumulation in the intima of arteries, results in the development of atherogenic plaques. In recent years, LDL-apheresis has proven to be an efficient treatment of hyperlipidemia in patients who do not respond sufficiently to diet and maximal lipid-lowering drug therapy.

LDL cholesterol reduction per treatment is approximately 60%, as well as serum levels of total cholesterol, triglycerides, apolipoprotein B (ApoB), Lp(a), fibrinogen are all significantly reduced [3].

In particular, Lp(a) has been identified as a risk factor for cardiovascular disease. In numerous pro-

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spective studies, elevations of plasma Lp(a) level, usually defined as $\leqslant$30 mg/dL, were significantly correlated with coronary artery disease (CAD) [4], mainly in the white population. Therapeutic treatments to lower Lp(a) are limited. The most effective method to reduce plasma Lp(a) concentration significantly is LDL apheresis [5]. It might exert its favourable action through numerous mechanisms and its ability to modify the serum level of many molecules might explain its utility and application in different diseases beyond lowering cholesterol therapy.

3. Anti-inflammatory action and endothelial dysfunction

Inflammation has been recognized as a major mechanism in atherosclerotic lesion formation [6] and C-reactive protein (CRP) has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty or those with acute coronary syndromes. These highly consistent clinical data are supported by abundant laboratory and experimental evidence that demonstrate that atherothrombosis, besides being a disease of lipid accumulation, also represents a chronic inflammatory process [7].

A therapeutic reduction of CRP might, therefore, reduce the risk of cardiovascular events. A single LDL apheresis lowers CRP by 20–65% [8]. Kobayashi et al. have shown that serum level of CRP decrease significantly after a single session of LDL apheresis as after 10 sessions when comparing the values recorded at the beginning of LDL apheresis [9].

The role of elevated fibrinogen levels as an independent risk factor for coronary, cerebral and peripheral vascular disease is well established on the basis of clinical and epidemiological studies [10]. Fibrinogen, like CRP, is an endothelial activation marker and endothelial dysfunction of the microcirculation is considered to be the main pathogenetic mechanism of diseases such as ischemic optic neuropathy (NAION), sudden hearing loss (SHL), pre-eclampsia and others. LDL apheresis, is able to significantly reduce fibrinogen (up to approximately 60% after the first procedure) levels in these case [11–13].

Selective LDL adsorption simultaneously removes circulating soluble adhesion molecules like intercellular and vascular cell adhesion molecules (sICAM-1 and sVCAM-1) [14], P-selectin, E-selectin, TNFalpha, monocyte chemoattractant protein-1 (MCP-1) and other various proinflammatory and procoagulatory factors [15,16].

Lipid-lowering therapy improves endothelium-dependent vasodilatation. There is experimental and clinical evidence that hypercholesterolemia leads to an impairment of endothelial function in coronary and cerebral arteries but a single LDL apheresis reverses this effect. Tamai et al. demonstrated that an immediate improvement in blood flow in response to acetyl choline is accompanied by a reduction in oxidized LDL and an increase in nitric oxide (NO) production [17].

Furthermore, in a study conducted on 35 hypercholesterolemic patients with angiographically documented CAD (demonstrated with PET scan, performed immediately before and 18–20 h after a LDL apheresis), Mellwig showed an improvement of myocardial blood flow, coronary flow reserve and a reduction of minimum coronary resistance [18] as confirmed by a study that suggested an enhanced release of NO from the endothelium consequent on adsorption of native and oxidized LDL by the DSA column [19].

An analogous improvement in NO-dependent vasodilation may explain the improved cerebral blood flow documented in FH patients after LDL apheresis as well as the increase in lower limb blood flow and regional myocardial perfusion observed in patients undergoing long-term treatment, although decreased blood viscosity may be another factor [20–22].

In 13 patients with CAD and hyperlipidemia [23], using a transcranial doppler sonography, Pfefferkorn observed a significant improvement of CO_2 reactivity after a drastic lowering of LDL cholesterol, lipoprotein(a) and fibrinogen levels.

Cattin, in the hypothesis that LDL apheresis could reduce the adhesive properties of monocytes to endothelium and therefore interfere with a key mechanism in atheroma formation, demonstrated that with LDL apheresis treatment there are: a reduction of 54% in oxidized LDLs, a significant increase of vitamin E concentration in LDLs (+14.2%; $p < 0.05$), but also a decrease of monocyte adhesion by approximately 61%. The variation became statistically significant