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Application of Lipoprotein Apheresis in Drug-Resistant Nephrotic Syndrome

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Application of Lipoprotein Apheresis in Drug-Resistant Nephrotic Syndrome

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Resumo

A aferese de lipoproteínas é um termo usado para descrever métodos de aferese que removem seletivamente lipoproteínas contendo apolipoproteína B [LDL, VLDL, Lp(a)]. O seu uso foi descrito pela primeira vez em 1974 para o tratamento da hipercolesterolemia familiar homozigótica, sendo usada até aos dias de hoje como primeira linha na prevenção de eventos cardiovasculares e na redução dos níveis de colesterol nestes doentes. Dada a sua elevada eficácia no tratamento de patologias associadas a elevados níveis de colesterolemia de difícil tratamento, tem havido um crescente interesse no estudo da sua aplicabilidade em diferentes áreas, nomeadamente na nefrologia, mais especificamente na síndrome nefrótica.

A síndrome nefrótica é classicamente descrita como proteinúria superior a 3,5 g/dia associada a hipoalbuminemia e a edema periférico. A hiperlipidemia e a suscetibilidade para doença trombótica estão frequentemente presentes. A síndrome nefrótica refratária, definida por uma condição patológica resistente ao tratamento com corticosteroides e outros fármacos imunossupressores, tem como entidades mais frequentes a glomerulosclerose segmentar e focal, a doença de lesões mínimas e a nefropatia membranosa. Os riscos associados às complicações da albuminúria grave têm motivado a procura e a investigação de terapêuticas novas, capazes de induzir uma remissão mais eficaz da proteinúria. Na verdade, a síndrome nefrótica refratária quando não tratada pode progredir para a doença renal crónica progressiva com necessidade de diálise ou de transplante renal, o que é especialmente preocupante em doentes jovens e crianças. A aferese das lipoproteínas, além de proporcionar uma excelente redução dos níveis de colesterol total, apresenta efeitos moduladores da inflamação, apresentando-se, desta forma, como uma possível hipótese de tratamento nestes casos.

Esta revisão aborda o sistema de aferese das lipoproteínas, as diferentes metodologias técnicas e as principais indicações. Além disso, o artigo foca a aplicabilidade deste tipo de aferese na síndrome nefrótica refratária, nomeadamente na glomerulosclerose segmentar e focal, na doença de lesões mínimas e na nefropatia membranosa, tanto na população adulta como pediátrica.

A revisão baseou-se na pesquisa nas bases de dados eletrónicas PubMed, MEDLINE e Embase, sem restrição pelo ano de publicação. Recorreu-se ainda à base de dados ClinicalTrials (www.clinicaltrials.gov) e às orientações KDIGO. O critério de seleção das publicações mais recentes foi a sua aplicabilidade à prática clínica. A última pesquisa foi realizada a 03/06/2020

Palavras chave: *"Drug-resistant nephrotic syndrome", "Lipoprotein Apheresis", "Focal segmental glomerulosclerosis", "Membranous nephropathy" e " Minimal change disease".*

Abstract

Lipoprotein apheresis is a term used to describe methods of apheresis which selectively remove lipoproteins containing apolipoprotein B [LDL,VLDL, Lp(a)]. It was first described in 1974 for the treatment of homozygous familial hypercholesterolemia and is still used nowadays as first line therapy in prevention of cardiovascular events and in the reduction of cholesterol levels in these patients. Given its high efficacy in treating difficult to control high-level cholesterol-associated conditions, there has been a growing interest in the study of the applicability of this method in different areas, namely nephrology, more specifically in nephrotic syndrome.

Nephrotic syndrome is classically described as proteinuria higher than 3.5 g/day associated with hypoalbuminemia and peripheral oedema. Hyperlipidaemia and susceptibility to thrombotic disease are frequently present. Refractory nephrotic syndrome, defined as a pathological condition resistant to treatment with corticosteroids and other immunosuppressive drugs, is most frequently related to entities as focal segmental glomerulosclerosis, minimal change disease and membranous nephropathy. The risks associated to the complications of severe albuminuria have motivated the search and investigation of new therapies, towards to induce a more effective remission of proteinuria. In fact, untreated refractory nephrotic syndrome can progress to chronic kidney disease requiring dialysis or kidney transplantation, which is especially distressing in young patients and children. Lipoprotein apheresis, in addition to significant decrease of cholesterol levels, presents modulatory effects in inflammation, creating a possibility of treatment in these patients.

This paper aims to assess the lipoproteins apheresis system, its different technical methodologies and main therapeutic indications. In addition, the paper focuses in the applicability of this type of apheresis in refractory nephrotic syndrome, namely in focal segmental glomerulosclerosis, in minimal change disease and in membranous nephropathy, both in the adult and paediatric population.

This review was based on the research in electronic databases such as PubMed, MEDLINE and Embase, without publication year restriction. Clinical Trials database (www.clinicaltrials.gov) and KDIGO guidelines were also used. The criteria for selection of the recent publications was the applicability to clinical practice. The last review was conducted on June 3, 2020.

Key-words: *"Drug-resistant nephrotic syndrome", "Lipoprotein apheresis", "Focal segmental glomerulosclerosis", "Membranous nephropathy" e "Minimal change disease".*

List of Abbreviations

ACEi: Angiotensine converting enzyme inhibitor
AKI: Acute Kidney injury
ALB: Serum albumin
Anti-PLA2R: Phospholipase A2 receptor
ApoB: Apolipoprotein B
ARB: Angiotensin receptor blocker
ASFA: American Society for Apheresis
AV: Arteriovenous
BK: Bradykinin
C3: Complement 3
CKD: Chronic kidney disease
Cr: Creatinine
CR: Complete remission
CRe: Complete relief
CyA: Cyclosporine A
DALI: Direct absorption of lipoprotein hemoperfusion
DAS: Dextran sulfate absorption
ESRD: End-Stage Renal Disease
FDA: Food and Drug Administration
FH: Familial hypercholesterolemia
FSGS: Focal segmental glomerulosclerosis
GFR: Glomerular filtration rate
GN: Glomerulonephritis
HDL: High density Lipoprotein
HELP: Heparin-induced precipitation
I.V.: Intravenous
INS: Idiopathic nephrotic syndrome
IRe: Incomplete relief
IR: Incomplete remission
KDIGO: Kidney Disease Improving Global Outcome
LA: Lipoprotein Apheresis
LDL: Low-density lipoproteins
LDL-A: Low-density lipoprotein apheresis
LLD: Lipid lowering drugs
Lp (a):Lipoprotein (a)
MCD: Minimal change disease
MN: Membranous nephropathy
NE : No effect
NO: Nitric oxide
NR: Nephrotic range
PCSK9 : Proprotein convertase subtilisin/kexin type 9
PSL: Prednisolone
PVT : Provastatine
RAS: Renin–angiotensin system
SGLT2: Sodium-glucose transport proteins 2
TC: Total cholesterol
TXA2: Tromboxane A2
UP: Urinary protein
VLDL: Very Low-density lipoproteins

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I. Definition and History of Lipoprotein Apheresis

Apheresis consists of an extracorporeal procedure that selectively removes abnormal cells or substances from a patient's blood in which the residual components are returned to the patient during or at the end of the treatment.[1] In nephrology it was first used to treat anti-glomerular basement membrane disease[2], being, until this day, the basis of the treatment to this disorder.[3] This technique has been also used in multiple medical fields aside from nephrology such as immunology, endocrinology and haematology with similar success.[4]

Lipoprotein apheresis is a term used to describe apheresis methods which selectively remove apolipoprotein B (apoB) containing lipoproteins specifically, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and lipoprotein (a) [(Lp (a)], over high-density lipoprotein (HDL).[4] Lupien et al. were the first to attempt this technique, while studying the effect of selective removal of LDL in patients with familial hypercholesterolemia (FH).[5] The technique involved the withdrawal of venous blood and its mixture with heparin-linked agarose beads prior to re-infusion.[4;5] During this process, apoB-containing lipoproteins selectively bonded with heparin-linked agarose forming complexes, allowing for later filtration of the bounded lipoproteins while the blood was being transfused back to the patient.[4;5]

Later, in 1981 Stoffel et al. modified the technique created by Lupien et al. calling it low--density lipoprotein apheresis (LDL-A). The technique consisted of prior separation of plasma from heparinised blood and its passage through two columns containing anti-LDL sepharose (immunoadsorbent). The two columns were used in rotation so that one column functioned as immunoadsorbent while the other column was being processed for apoB-containing lipoproteins, allowing for much faster and efficient sessions. However, despite being named LDL-A, the application of this term is not the most appropriate as it removes not only LDL, but other apoB-containing lipoproteins. Therefore, nowadays the most correct term for this procedure is lipoprotein apheresis (LA).[4-7]

II. Lipoprotein Apheresis Methods

There are four basic methods of LA: anionic column-based adsorption, heparin-induced precipitation, size-based filtration, and immuno-affinity-based binding. All of these techniques are similarly effective and well tolerated with the average immediate LDL cholesterol concentration reduction approximately 50–60 % of the original levels, with minimal decrease of HDL (except size-based filtration). Venous blood is utilized and anticoagulation is required. Some methods require plasma (immunoadsorption, size-based filtration, dextran sulfate absorption and heparin-induced precipitation) while others utilize whole blood (direct adsorption of lipoprotein using hemoperfusion). However, only two of these systems are currently FDA-approved: dextran sulfate absorption, a type of anionic column-based adsorption (Liposorber® LA- 15 system), and heparin-induced precipitation (Plasmat® Futurea).[4;7;8]

1. Anionic Column-based Adsorption

This method is divided into two systems: dextran sulfate absorption (DSA) and direct absorption of lipoprotein hemoperfusion (DALI).

a) DSA

This technique is widely used, especially by the FDA-approved Liposorber LA-15® system. The system consists of two negative charged dextran sulfate columns through which heparinized plasma is passed. ApoB, which is positively charged, non-covalently binds to the polyanionic dextran sulfate absorber allowing the selective removal of apoB-containing lipoproteins. A schematics of this system is represented in Figure 1.[4;8-10]

b) DALI

Conventional LA requires initial separation of plasma from blood cells. On the other hand, this system allows for the removal of apoB-containing lipoproteins directly from whole blood, substantially simplifying the procedure. This technique also uses negatively charged columns but the absorber has small pores that allow the passage of essential blood constituents. Despite being a safe and effective proved system, it is not yet FDA-approved.[4;10-12]

2. Heparin-induced Precipitation (HELP)

HELP consists of the process of precipitating apoB-containing lipoproteins in an acid environment by adding acetic-acid. The precipitated lipoproteins are filtered from the plasma and pH is restored before being mixed with the remaining blood and returned to the patient.[10;13;14]

3. Membrane Differential Filtration (Double Filtration Plasmapheresis)

Membrane differential filtration is a non-FDA-approved system that involves the depletion of lipoproteins from plasma based on their molecular weight and three-dimensional size. Although LDL reduction is comparable to other FDA-approved methods, sized based filtration is less selective in such a way that it depletes important plasma components (e.g. HDL by 25-42%).[4;15;16]

4. Immuno-adsorption

This technique, first described by Stoffel et al., uses two columns containing polyclonal sheep antibodies to human apoB with sepharose 4B gel.[10] The passage of plasma through these columns selectively remove apoB-containing lipoproteins.[10;17] This non-FDA approved system is the most selective methodology among the various LA technologies but may be less safe due to leaking of the sorbent into the returned plasma, which could cause febrile or anaphylactic reactions.[4;17;18]

III. Technical Aspects of Lipoprotein Apheresis

1. Kinetics of Lipoprotein Depletion and Resurgence

While performing LA, levels of apoB-containing lipoproteins decrease acutely by 50–60% of pre-treatment levels, beginning to increase shortly after the end of the treatment and reaching a plateau within a week nonetheless, levels don't return to pre-treatment values. If optimally spaced, long term therapy reports show that an average reduction of LDL levels of 25-60% can be achieved.[19-21]

2. Treatment Goal, Duration and Frequency

For the most commonly used LA system, FDA-approved Liposorber® LA-15, a total of 12 sessions distributed through 9 weeks (twice per week for 3 weeks then once per week for 6 weeks) are recommended. The goal of this therapy is to reduce the time-averaged total cholesterol (TC) and LDL by > 50% and > 60%, respectively. Acute reductions of > 65% and > 70% for TC and LDL, respectively, must be achieved during each session to reach these time-averaged goals.[4]

3. Vascular Access

Access to blood flow must be reliable, safe and satisfactory to the patient. The success of vascular access strategies is likely to have a significant impact on patient tolerance and compliance to treatment. Options for vascular access in LA include peripheral venous cannulation, central venous catheterisation and use of arteriovenous (AV) fistula or graft.[22;23]

As procedures are typically run at a blood withdrawal rate of 75 ± 10 mL/min, in many adult patients, peripheral veins can adequately support these flow rates and two peripheral veins, typically antecubital veins, are used for blood withdrawal and return. On the other hand, smaller patients usually require placement of long-term venous catheters to initiate therapy.[22;23]

Despite being the most popular long-term choice, peripheral vein access is not the most effective vascular access, with AV-fistula being the optimal method. Over time, as peripheral veins continue to be used for this treatment, their success at providing a reliable access diminishes. In such patients, timely anticipation of access difficulties will allow planning for the creation of an AV-fistula to minimize treatment interruption.[22;23]

Unfortunately, according to Doherty et al., in a substantial percentage (37%) of patients treated with LA, AV-fistula fails to function.[24] Central venous catheters may also be used, but these are not ideal long-term solutions, given the risk of infection and thrombosis.[25]

IV. Clinical Aspects of Lipoprotein Apheresis

1. Indications

LA was originally used for FH treatment, which is a autosomal dominant condition associated with premature cardiovascular disease (eg. acute myocardial infarction at a relatively young age), abnormally elevated LDL (eg. *arcus lipoides*), and, sometimes, Lp(a) plasma levels.[26] Today, according to 2019 ASFA Guidelines on the Use of Therapeutic Apheresis in Clinical Practice, LA is indicated in a much larger number of diseases, including steroid resistant focal segmental glomerulosclerosis (FSGS), as presented in *Table I*.[4]

2. Benefits

In addition to directly reducing levels of atherogenic lipoproteins [LDL, VLDL, and Lp(a)], it has been proposed that LA has additional benefits through modulatory effects on inflammation and rheology. Several studies have shown that different kinds of substances are retained by these systems, including the expected lipoproteins, as well as adhesive, rheologically relevant and inflammation-related proteins. Some of these effects include the amelioration of corticosteroid response, a decrease in transthyretin, interleukin-1b and fibronectin levels, of tromboxane A2 production and also in a variety of coagulation factors, as well as an increase in nitric oxide and bradykinin production as presented in *Table II*.[27-35]

Overall the potential benefits of retaining these molecules include: anticoagulant effect, improvement in renal haemodynamics, suppression of intraglomerular invasion of macrophages, decrease pro-inflammatory state and enhancement of response to immunosuppressant. These benefits explain why LA may play an important role in nephrotic syndrome treatment.[27-35]

3. Absolute Contraindications and Side Effects

Important contraindications exist and their knowledge is mandatory before beginning LA. The contraindications of the FDA-approved Liposorber® LA-15 system are described in *Table III*.[36] Side effects are similar to any extracorporeal system (eg. hypotension, infection/bacteraemia, nausea, vomiting, angina, fainting, vertigo, shivering, headaches and diaphoresis), still they are generally well tolerated and serious side effects are extremely rare.[37;38] Heigl et al., found that in a total of 36745 treatments using different types of LA systems, only 1,1% had adverse effects, the most common being hypotension (53%) and prolonged bleeding or hematoma (30%).[39] Moreover, only 23,5% (0,3% overall) were severe enough to terminate the session.[39]

V. Nephrotic Syndrome Management

Nephrotic syndrome presents with four classic features: heavy proteinuria, greater than 3.5 g/day, associated with hypoalbuminemia, hypercholesterolemia and oedema. Other features, such as, hypertension and a hypercoagulability state, may also be present. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in glomerular filtration rate (GFR), resulting in renal failure. The rate of progression to end-stage renal disease (ESRD) is directly associated with the amount of 24-h urine protein excretion, as such, higher proteinuria induces a faster decrease in GFR.[41-45]

In general, for the diagnosis of glomerular disease/glomerulonephritis (GN), a renal biopsy is mandatory. The single exception to this rule is steroid sensitive nephrotic syndrome in children, where biopsy is recommended if there is an atypical clinical response.[46]

1. Immunosuppressive Role in Nephrotic Syndrome Treatment

Immunosuppressive treatment plays an essential role in the nephrotic syndrome management and varies depending on the histopathologic entity. The focus in the management of chronic patterns of GN is no longer to attempt to achieve a cure, but instead to try to control the disease. This paradigm has translated into the use of more extended or repeated treatment regimens with different drugs aiming to control the disease and at the same time managing nephrotic syndrome complications.[46]

2. Managing Complications

a) Hypertension

Hypertension is a common complication in nephrotic syndrome, as in most types of chronic kidney disease (CKD). The objective of blood pressure management is both to protect against the cardiovascular risks of hypertension and to delay progressive loss of GFR. According to 2018 ESC/ESH Guidelines for the management of arterial hypertension, it is recommended, for most patients, if well tolerated, a target blood pressure of 130/80 mmHg or less. In case of being a child with GN, blood pressure should be below the 50th percentile for systolic and diastolic pressure according to age and sex.[43;46-49]

Lifestyle modifications (salt restriction, weight normalization, regular exercise, and smoking cessation) are an essential part of blood pressure control and should always be applied in conjunction with pharmacological therapy. Nowadays, according to 2018 ESC/ESH Guidelines for the management of arterial hypertension, it is recommended a dual combination of an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB)

associated with a calcium channel blocker (CCB), within a single pill. Despite being the same combination of drugs used in uncomplicated hypertension, ACEi and ARB are essential in controlling CKD, not only to control hypertension but also to decrease proteinuria, slowing the progression of kidney disease.[43;46-49]

b) Proteinuria

Reduction in proteinuria remains a goal in virtually all glomerular diseases, as it reflects control of the primary disease and reduces glomerular hypertension, contributing to the reduction of podocyte damage, an important factor in renal scaring. In nephrotic syndrome, a reduction of proteinuria to a non-nephrotic range often results in an elevation of serum proteins to normal levels (particularly albumin). This elevation, in turn, alleviates many of the patient's symptoms as well as the metabolic complications of the nephrotic syndrome, thus improving quality of life. The antiproteinuric agents of choice are ACEis or ARBs, which may reduce proteinuria by up to 40–50% in a dose-dependent manner, particularly if the patient complies with dietary salt restriction. Currently, several large studies report possible usage of sodium-glucose transport proteins 2 (SGLT2) inhibitors as a new strategy of proteinuria reduction.[46;49-52]

c) Nephrotic Oedema

The mainstay of treating nephrotic oedema is the use of loop diuretics accompanied by moderate dietary sodium restriction. Unfortunately, nephrotic patients are often diuretic-resistant even if GFR is normal. As such, the diuretic dose frequently has to be increased and an association of loop diuretics and thiazides is often necessary to manage oedema in these patients. As a last resort, in cases of refractory volume overload haemodialytic therapy is recommended.[46]

d) Thrombotic Events

The risk of thrombosis is inversely related to the serum albumin values. As values fall below 2 g/dL, greater is the probability of thrombotic events. The gain from prophylactic anticoagulation (e.g. heparin 5000 units subcutaneously twice daily) depends on the possibility of thrombotic events, the potential of anticoagulation to impede such issues, and the bleeding risk related with anticoagulation.[46;49]

e) Infection

A high order of clinical vigilance for bacterial infection is vital in nephrotic patients. Infectious complications include recurrent respiratory tract infections, urinary tract infections, peritonitis, and sepsis, particularly with encapsulated bacteria such as *Streptococcus pneumonia*. Therefore, all patients should receive pneumococcal vaccination as well as the annual influenza vaccination.[46;49]

VI. Role of Dyslipidemia in Nephrotic Syndrome

Abnormal lipid metabolism is prominent in nephrotic syndrome and some of those abnormalities are presented in *table IV*.[53-55] Although nephrotic syndrome can affect LDL synthesis, as low oncotic pressure directly stimulates hepatic *APOB* gene transcription, it is thought that the levels of most apoB-containing lipoproteins are altered owing to decreased clearance.[55-57]

Many of the complications of NS, including the increased risk of atherosclerosis and thromboembolism, can be linked to the dysregulated lipid metabolism and dyslipidaemia. Moreover, there seems to be a correlation between the extent of altered lipid metabolism and the magnitude of proteinuria, as the lipid nephrotoxicity hypothesis suggests.[58;59]

1. Lipid Nephrotoxicity Hypothesis

The lipid nephrotoxicity hypothesis proposes that hyperlipidaemia, in addition to proteinuria and hypoalbuminemia, leads to adverse and injurious effects in kidneys and may cause glomerulosclerosis similar to atherosclerosis.[60]

After an initial glomerular injury, likely to be inflammatory, a series of self-perpetuating events occur. In patients with renal disease, lipoprotein particles undergo oxidative modification, resulting in the formation of small lipoproteins and enhanced synthesis of oxidized LDL. Circulating LDL binds to glycosaminoglycans in the glomerular basement membrane, increasing its permeability and therefore, increasing urinary albumin and perpetuating glomerular damage. Foam cells derived from macrophages, vascular smooth muscle cells, and mesangial cells engulf modified and unmodified LDL resulting in increased proliferation and cell damage, contributing to glomerulosclerosis.[59;60]

Furthermore, proximal tubules reabsorb a portion of the filtered lipoprotein. However, as glomerular damage progresses, large amounts of lipoprotein reach the tubular lumen and cannot be reabsorbed. The remaining lipoproteins, which progress through the nephron are altered and If intraluminal pH is close to the isoelectric point of the apolipoprotein, they will precipitate inside the tubular lumen, causing tubulointerstitial disease. Moreover, dyslipidaemia induces systemic vascular endothelium injury, which contributes to atherosclerosis and hypertension.[59;60]

All these mechanisms in conjunction allow for self-perpetuating glomerular and tubulointerstitial damage that culminates with ESRD, as simplified in Figure 2.[59;60]

2. Managing Lipid Abnormalities

The goal of serum LDL in patients with coronary disease or a coronary equivalent, such as chronic kidney disease, is less than 70 mg/dL (1.8 mmol/L). Dietary restriction of fats and cholesterol alone has only modest effects on hyperlipidaemia in glomerular disease, in particular in nephrotic syndrome. Although traditionally statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) have been used to treat hyperlipidaemia and are effective, target values may not be achieved, especially in the new era of very low LDL target levels. The lipid abnormalities induced by the nephrotic syndrome reverse with the resolution of the disease, as with corticosteroid therapy in minimal change disease.[46;49]

VII. Drug Resistant Nephrotic Syndrome

The term drug-resistant, in general, refers to the patient who remains in nephrotic range (NR), defined as estimated 24-hour urinary protein (UP) ≥ 3.5 g/day, after initial immunosuppressive treatment, or it can also be applied to patients that relapse and relief from NR cannot be achieved with first or second-line treatment. The definition of drug-resistant nephrotic syndrome is very controversial, as different authors use different treatment durations and drugs for different nephrotic syndrome entities. For example, KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis, only defines steroid-resistant nephrotic syndrome and, in the specific case of FSGS, it is defined as persistent proteinuria despite prednisone 1 mg/kg/day or 2 mg/kg every other day for more than 4 months.[46] On the other hand, in Japan, where most of the LA studies have been conducted, drug-resistant NS is defined as the inability to achieve remission after primary medication, which is generally full-dose steroids (1 mg/kg/day) or cyclosporine A treatment for at least 4 weeks.[61]

As expected, different remission criteria also exist. In Japan and in most LA studies, a 4-category scale is most commonly used, depending on the amount of estimated 24-hour UP: complete remission (undetectable UP); incomplete remission type I (UP < 1.0 g/day); incomplete remission type II (UP ≥ 1 and < 3.5 g/day) ; and no effect (UP ≥ 3.5 g/day).[61] On the other hand, KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis uses different definitions depending on each entity of nephrotic syndrome.[46]

The most commonly referred drug-resistant nephrotic syndromes are three different entities summarized under the umbrella term idiopathic nephrotic syndrome (INS), which represent 30% of all glomerulopathies. The most frequent anatomopathological presentations of INS are minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN). While the frequency of MCD is decreasing in adulthood, FSGS prevalence remains stable and MN is increasing at an advanced age.[62-64]

Unfortunately, despite several advances in INS pathophysiology, idiopathic MCD and FSGS remain complex diseases for which new therapies are needed, as clinical evolution is still unpredictable.[62] As explained earlier, persistent nephrotic range correlates with renal damage. Therefore, these cases are usually associated with rapid progression to ESRD, leading to the necessity of renal transplant or initiation of hemodialysis, which is especially problematic in children.[65;66] In fact, resistance to corticosteroids and immunosuppressive therapy is now considered the strongest predictor of ESRD.[46]

1. Idiopathic Primary Focal Segmental Glomerulosclerosis.

FSGS is now one of the most common patterns of glomerular injury encountered in human kidney biopsies, both in children and in adults, and it is the most common cause of nephrotic syndrome in the african american and US hispanic populations.[67;68] A kidney biopsy is always recommended as certain characteristics allow for the identification of this lesion.[46] Some of these features include: segmental increase of mesangial matrix with obliteration of the capillaries, sclerosis, hyalinosis, and segmental scarring of nephrons.[68]

In most cases of Idiopathic FSGS, the natural history of the disease is prolonged and quite variable with some reports showing that only 47-65% actually respond to initial treatment and up to 40% of complete remitters may have a relapse. Unfortunately, the non-responsive and relapsed patients do not have a good prognosis, having 5 and 10-year kidney survival averaging 65% and 30%, respectively.[69-71]

Treatment: KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis recommends, as initial therapy, prednisolone 1 mg/kg/day (up to a maximum of 80 mg/day) or alternate-day prednisone 2 mg/kg (up to 120 mg) for at least 4 weeks and for a maximum of 4 months.[46]

In case of steroid-resistant idiopathic FSGS, defined as persistent proteinuria after initial treatment, cyclosporine at 3–5 mg/kg/day in divided doses is recommended to be given for at least 4–6 months, though, a combination of mycophenolate mofetil and high-dose dexamethasone is also appropriate. In case of remission, treatment continuation is recommended for 1 year but if no remission is achieved by the sixth month, cyclosporine should be discontinued.[46]

Complete remission is defined as a reduction of proteinuria to <0.3 g/day, with normal serum creatinine and serum albumin (>3.5 g/dL).[46]

Partial remission is defined as a reduction of proteinuria to 0.3–3.5 g/day, stable serum creatinine (change in creatinine <25%).[46]

2. Minimal Change Disease in Adults

MCD represents about one fourth of NS in adult patients and refers to the occurrence of nephrotic syndrome with no glomerular lesions by light microscopy (or only minimal mesangial prominence), no staining on immunofluorescence microscopy (or low-intensity staining for C3 and IgM), and foot process effacement but no electron-dense deposits on electron microscopy.[72] MCD in children is extremely sensitive to corticosteroids, on the other hand, adults tend to respond in a more slow and unpredictable way. Actually, only about 75% of patients respond to treatment and that may be occur as late as 3-4 months after treatment

initiation.[46] Moreover, relapses are common in adult patients, with some patients becoming steroid-resistant. However, progressive CKD is not part of the natural history of adults with MCD, and its occurrence suggests underlying FSGS.[73;74]

Treatment: KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis recommends a daily single dose of 1 mg/kg (maximum 80 mg) of prednisone or an alternate-day single dose of 2 mg/kg (maximum 120 mg), until complete remission (minimum 4 weeks to a maximum of 16 weeks). If steroid-resistance occurs (persistence of proteinuria despite prednisone 1 mg/kg/day or 2 mg/kg every other day for >4 months), revaluation of the patient for different causes of nephrotic syndrome is recommended and as such, a kidney biopsy is recommended. In case of true steroid-resistant MCD to initial therapy, KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis doesn't have recommendations for inducing remission.[46]

3. Idiopathic Membranous Nephropathy

Membranous nephropathy is the most common cause of NS in caucasians and its evolution is also variable. In fact, one third of patients enter spontaneous remission with blockade of the renin-angiotensin system and one third develop a persistent nephrotic syndrome, while another third of patients develop end-stage kidney disease. The diagnosis of IMN is made by exclusion of secondary causes (systemic erythematosus lupus, chronic hepatitis B infection, drugs and malignancy) and by careful examination of the kidney biopsy by light, immunofluorescence, and electron microscopy. Diagnostic features in biopsy include capillary wall thickening, normal cellularity, IgG and C3 along capillary walls on immunofluorescence, and subepithelial deposits on electron microscopy. Moreover, in IMN, deposition of the IgG4 subclass of IgG is dominant (anti-PLA2R), whereas other IgG subclasses dominate in secondary forms of MN.[75-77]

Treatment: About a third of patients with IMN undergo spontaneous remission of nephrotic syndrome. Therefore, it is reasonable to delay specific therapy for at least 6 months while utilizing supportive therapy, including ACEis or ARBs.[46]

As such, KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis only recommends treatment of IMN nephrotic syndrome with immunosuppressive agents if urinary protein excretion persistently exceeds 4 g/day, remains at over 50% of the baseline value, and does not show a progressive decline during antihypertensive and antiproteinuric therapy for at least a 6 month period.[46]

KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis recommends initial therapy with a 6-month course of alternating monthly cycles of intravenous methylprednisolone (1 g/day for 3 days) associated with oral methylprednisolone (0.5 mg/kg/day for 27 days), and

oral chlorambucil (0.15-0.2 mg/kg/day) or cyclophosphamide (2.0 mg/kg/day). After initial treatment, a 6-months period of conservative management is recommended before treatment failure is considered. In case of IMN resistant to initial therapy, a calcineurin inhibitor is recommended as next therapy (cyclosporine or tacrolimus).[46]

4. Steroid Resistant Nephrotic Syndrome in Children

About 80% of children with nephrotic syndrome achieve complete remission with corticosteroids, as such, a kidney biopsy is not usually recommended at presentation. Even if relapse occurs there is a very high chance that it is corticosteroid-sensitive, still, in a small percentage of children, steroid-resistant nephrotic syndrome may occur, and it is defined as failure to achieve complete remission after 8 weeks of corticosteroid therapy. In these patients a kidney biopsy is recommended to exclude secondary causes of nephrotic syndrome, and assess the extent of interstitial and glomerular fibrosis.[46;78]

Treatment: KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis recommends using a calcineurin inhibitor combined with low dose corticosteroids as initial therapy for children with SRNS, by a minimum of 6 months if complete remission is achieved, and 12 months if partial remission is achieved by the sixth month. Alongside immunosuppressive treatment the use of ACEis or ARBs is recommended. In the case of absence of remission with initial therapy, mycophenolate mofetil is recommended or as an alternative, high-dose corticosteroids or a combination of these agents can be also used.[46]

SRNS generally, and specially FSGS, is associated with a 50% risk for ESRD within 5 years of diagnosis if patients do not achieve a partial or complete remission.[79] Children reaching ESRD have, on average, a reduced life expectancy of about 19 years following initiation of dialysis.[80] At times, in these patients, the only possible therapy is trying to slow down the progression to ESRD with renal protective drugs, such as ACEis or ARBs.[80]

As KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis shows, different drugs can be used in these patients. However, in most cases, long duration therapies are needed to achieve partial or complete remission and in some, unfortunately, no improvement at all is noted. Moreover, chronic immunosuppressive therapy has important side effects, and its potential benefits need to be weighed against the impact on patient mortality, morbidity and quality of life.[46] LA's role is to try to improve these patients' outcome, potentially inducing partial or even complete remission.

VIII. Clinical Efficacy of Lipoprotein Apheresis in Idiopathic Nephrotic Syndrome

Investigations with LA have been reported mainly in Japan. Although many of these reports are prospective one-branched studies and case reports, the clinical efficacy of this technique to induce and maintain remission is promising, as presented in *Tables V and VI.*

Since 1994, Muso et al. have tried to evaluate the benefits of LA in steroid and drug-resistant nephrotic syndrome.[81-86] In their first study, they observed that a combined therapy of LA with corticosteroid pulses managed to induce complete remission in 4 out of 8 patients with steroid resistant INS. Of the remaining four, one had incomplete remission and 3 were resistant but, even so, a slight creatinine clearance increase was observed in all patients (73.8 ± 30.9 mL/min to 82.6 ± 39 mL/min).[81]

In 2000, Stenvinkel et al. performed a prospective study with seven patients with INF that would be treated with LA as monotherapy. Following treatment, 6 responded with a small increase in albumin and a 30-40% decrease in lipoproteins and total cholesterol. However, 6 weeks after the end of therapy, lipoprotein and total cholesterol levels returned to baseline. On the other hand, during a one-year follow-up of 5 of these responders, a small but significant ($P<0.05$) increase in serum albumin levels was noted in all five patients.[82]

In 2001, Muso et al. conducted a comparative study in patients with steroid-resistant nephrotic syndrome. This study compared a group of 17 patients treated with a combination of LA and full-dose steroids and another group of 10 patients treated only with full-dose steroids. Indeed, 2 weeks after treatment, in the LA group, 47% of patients presented relief of NR and after a 2-year follow-up, 76% achieved complete remission or type I incomplete remission. On the other hand, in the control group, only 20% and 22% achieved relief of NR and complete remission or type I incomplete remission, respectively. In addition, the time needed to decrease UP and the dose of steroids needed to achieve remission were lower in the LA group than they were in the control group.[83]

A large multicenter prospective study, POLARIS (Prospective Observational Survey on the Long-Term Effects of LA on Drug-Resistant Nephrotic Syndrome) conducted by Muso et al. evaluated the short and long-term effect of LA in 44 patients with drug-resistant nephrotic syndrome. In a short-term outcome, although 53.1% responded to the treatment, having been relieved of NR, only 21.3% achieved urinary protein levels <1.0 g/day. However, after a 2-year follow-up, 72.7% of patients were relieved from NR and more than one third of these achieved complete remission. Being a large multicenter study and given the fact that idiopathic FSGS was the most frequently studied entity of INS, Muso et al. tried to include a large portion of non-FSGS patients. In fact, this study is one of the few in which nearly half of the patients were non-

FSGS. Given the similar amount of FSGS and non-FSGS patients, Muso et al. managed to conclude that there seems to be no significant difference in the therapeutic effect of LA between FSGS and non-FSGS NS.[84;85]

1. Focal Segmental Glomerulosclerosis

The effect of LA in idiopathic FSGS is the most common study subject within drug-resistant nephrotic syndrome. In fact, as explained before, idiopathic FSGS has one of the highest rates of progression to ESRD, both in children and in adults. Recent studies have been made to try to evaluate the effect of LA specifically in this type of INS (*Table VI).*[86-88]

In 2007, Muso et al. conducted a prospective study with only drug-resistant FSGS patients with the objective of evaluating the long-term outcome (second and fifth year post-treatment) of LA combined with immunosuppressive drugs (steroid-35 patients; CyA-3 patients; Other ISD-8 patients). After the second year of follow-up, 90% of patients were relieved of NR, with almost half of them achieving complete remission (undetectable UP). At the fifth year of follow-up 93% of patients were relieved of NR, with more than half of these patients achieving complete remission.[86]

Considering only the paediatric population, Hattori et al. retrospectively studied the potential benefit of LA conjugated with prednisone in children (10.9 ± 2.7 years-old) with drug-resistant FSGS. They reported that after a follow-up of 4.7 ± 3.7 years, 54.5 % of patients were relieved of NR and 80% of these achieved complete remission. Raina et al. also reported clinical significance of LA in the paediatric population.[87;88]

Many case reports (*Table VII*) show that LA, either alone or combined with immunosuppressive treatment, has clinical benefits, both in adults and children with idiopathic FSGS. Kawasaki et al. managed, by combining LA with low-dose prednisolone, to achieve complete remission after a 12-year follow-up, in a 13 year-old child. On the other hand, Yokoyama et al. despite using LA as monotherapy, managed to achieve partial remission in an adult patient.[89-92]

2. Idiopathic Membranous Nephropathy

Idiopathic membranous nephropathy (IMN) is a common cause of NS in elderly patients and, as in all cases of NS, complications occur. However, given the increased comorbidities in elderly people, a rapid resolution to avoid complications of NS is needed. This is especially problematic in patients with massive proteinuria, hyperlipidaemia and high serum creatinine, as they drastically increase the rate of progression to ESRD.[46]

As such, Koshi-ito et al. investigated the potential benefit of LA when associated with steroids as initial induction therapy for IMN in older patients. Their study compared a group of 11 patients, to whom an average of 3.45 sessions of LA were applied, and a control group of 27 patients that would be treated with conventional steroid therapy. The different effects of the treatments were evaluated after 4 and 8 weeks of treatment. The reduction in UP and LDL and increase in albumin were significantly better in the LA group after both 4 and 8 weeks. Furthermore, the amount of prednisolone used after 8 weeks was significantly less in the LA group (p=0.027). On the other hand, the time required for remission between the two groups did not show any significant difference. Also, the amount of patients that achieved complete, type I partial or type II partial remission was the same in both groups.[94]

Yabuuchi et al. described a 61-year-old man that had been treated for 2 years with multiple immunosuppressive drugs, after which it was decided to initiate LA. After 9 years of LA with a frequency of two sessions per month (203 sessions in total) the patient's proteinuria was reduced to less than 1 g/day and no relapses occurred during the five years of follow-up.[95]

Sato et al. reported 3 cases (35, 75 and 76 years-old) of drug-resistant IMN treated with LA as an adjuvant of immunosuppressive therapy. All of these patients had a high-risk of renal failure and at least 6 months of persistent proteinuria before initiating LA. LA was performed once a week up to 5-7 times, associated with PSL plus CyA therapy. Impressively, two of these patients achieved complete remission. The third patient responded well after treatment, with continuous reduction of proteinuria, but unfortunately, after an abdominal surgery, the patient had a relapse and remission could not be achieved.[96]

3. Idiopathic Minimal Change Disease

Most reports of idiopathic MCD are included in studies of INS in general, and a large number of these reports show that LA has a potential clinical benefit in both children and adults with nephrotic syndrome.[81-85]

A case report from Kobayashi et al. describes a 17 year-old patient with relapsed minimal-change disease in whom 4 sessions of LA reduced proteinuria from 9.2 g/day to 0.2 g/day over a 38-day period, without any additional medication (apheresis was chosen over steroids due to the fact that serum titer of HBV was elevated, to prevent the risk of steroid-induced fulminant hepatitis). In fact, complete remission was maintained throughout the one-year follow-up period, without the need of any additional therapy.[97]

Okada et al. described a case of a 20-year-old with IMCD who had a relapse just 2 months after remission was induced by using PSL and CyA. In order to induce remission once

more, CyA dose was increased, but no effect was noted. As such, it was decided to add 6 sessions of LA, concomitantly with the administration of CyA. UP underwent a remarkable reduction and the patient was free of disease.[98]

IX. Conclusion

Lipoprotein apheresis emerges in nephrology as a potential treatment for patients with drug-resistant nephrotic syndrome in whom difficult to control complications comprise a rapid decline of renal function, an increase in morbidity, mortality and a decrease in quality of life.

The actual mechanism of actuation of LA in nephrotic syndrome is not totally understood, as it can help to induce remission when combined with immunosuppressive drugs, or it can act directly on the pathophysiological basis of NS by directly reducing renal damage. This lack of knowledge is due to the fact that most studies use LA combined with other therapies and only a few reports and case control studies actually apply LA as monotherapy. In fact, some authors proposed that LA has a more important role when associated with immunosuppressive therapy than when applied as monotherapy.

Multiple studies show that, in the majority of patients, an important relief of nephrotic range is achieved, shortly after being treated with LA. Furthermore, a significant portion of treatment-responders present complete remission and maintain this state for some years post-treatment. In fact, LA provides, not only, an immediate reduction of apoB-containing lipoproteins and total cholesterol, but also an increase of serum albumin and decrease in urinary protein and serum creatinine. Overall, a significantly lower dose of immunosuppressive therapy is required to achieve remission when LA is used. This is especially beneficial, since it allows for a decrease in the amount of side effects associated with these drugs. Nonetheless, it is important to point out that several limitations compromise these reports:

1. Some of the difficulties related to the research of these pathologies are due to the fact that they are less common entities, limiting prospective randomized studies or clinical trials in large series. Moreover, most of these reports don't apply LA as monotherapy. As such, despite showing promising results, it is difficult to directly associate LA with the favorable outcome.

2. The drug-resistant definition is too general in most of these studies, as it only includes a one-month therapy duration. As KDIGO 2012 Clinical Practise Guideline for Glomerulonephritis detailed, idiopathic nephrotic syndrome is a difficult-to-treat disease and long-term therapy is needed before proposing that a patient is resistant to treatment. Due to that, and as many of these reports are single-arm studies, it is difficult to differentiate the effect of LA from that of the immunosuppressive therapy, or if LA actually has any effect on these patients. Moreover, the potential for spontaneous remission is also not taken into account, and this can be especially important in idiopathic membranous nephropathy.

3. Aside from the POLARIS study and case reports, most studies only include a small amount of non-FSGS patients. Although results seem to show no difference in LA efficacy between different entities of INS, given the extremely small amount of studied patients, it is hard to be certain.

4. Follow-up time is very short, since most studies present final outcomes after only one or two years. In spite of these reports showing that remission is maintained after that amount of time, longer follow-up durations are necessary to evaluate the true effect of LA.

5. LA treatment durations vary depending on the study. In spite of the recommendations of a total of 12 sessions distributed through 9 weeks, some authors don't apply this regimen. As such, it is difficult to say if, in the investigations in which it was applied for several months, LA provided any benefit to these patients. On the other hand, it is also important to reflect if LA could´ve allowed for better results in the studies in which a total of 12 sessions was not reached.

Overall, LA is a promising therapy in children and adults with idiopathic nephrotic syndrome, in whom immunosuppressive therapy does not allow for an improvement of nephrotic range or carries strong side effects and risk for the patient. Nonetheless, there are a relatively low number of reports, and more studies are required in order to confirm the proposed benefits of this treatment. Although more prospective cohort studies with larger numbers of patients, longer follow-up periods and more uniform patient selection are needed, LA may truly represent a new hope for a rescue therapy.

X. Tables

Table I. Current indications of Lipoprotein Apheresis

Disease		Category	Grade
Familial hypercholesterolemia	Homozygotes	I	1A
	Heterozygotes	II	1A
Focal segmental glomerulosclerosis (FSGS) -Recurrent in kidney transplant/ Steroid resistant in native kidney		II	2C
Hypertriglyceridemic pancreatitis	Severe	III	1C
	Prevention of relapse	III	2C
Lipoprotein(a) hyperlipoproteinemia-Progressive atherosclerotic cardiovascular disease		II	1B
Peripheral vascular diseases		II	1B
Phytanic acid storage disease (Refsum's Disease)		II	2C
Sudden sensorineural hearing loss		III	2A

Levels of evidence are presented as Category and Grade:

Category I—disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatments; Category II—disorders for which apheresis is accepted as a second-line therapy, either stand-alone or in conjunction with other modes of treatments; Category III—optimum role of apheresis therapy is not established. Decision making should be individualized; Category IV—disorder in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. GRADE 1—strong recommendation; GRADE 2—weak recommendation; GRADE A—based upon high quality of evidence; GRADE B—based upon moderate quality of evidence; GRADE C—based upon low quality of evidence. [4]

Table II. Pleiotropic Effects of Lipoprotein Apheresis

Decrease in oxidized LDL;	Decrease in transthyretin;
Decrease in blood viscosity (IgM, fibrinogen, von Willebrand factor)	Decrease in variety of coagulation factors (e.g. VIII, IX, V, VII, X,)
Decrease in kininogen 1	Decrease in PCSK9 levels
Decrease in α1-antitrypsin	Decrease in fibronectin
Decrease in interleukin-1β	Increase in NO, BK production
Amelioration of corticosteroid response	Decrease fo TXA2 production

BK- Bradykinin; LDL- Low-Density lipoprotein; NO- Nitric oxide; PCSK9- Proprotein convertase subtilisin/kexin type 9; TXA2- Tromboxane A2.[27-35]

Table III. Absolute Contraindications of Liposorber® LA-15 System

Treatment with ACEi within the past 24 hours
Inability to achieve adequate anticoagulation (e.g. haemophilia, severe haemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery)
Inability to tolerate extracorporeal circulation therapy with Liposorber® LA-15 system (e.g. severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, stroke, or severe uncontrollable hypertension or hypotension)
Hypersensitivity to dextran sulphate cellulose, heparin or ethylene oxide

ACEi- Angiotensine converting enzyme inhibitor.
Adapted from LA-15 SYSTEM Operator's Manual No.1002en-Rx

Table IV. Lipid Abnormalities Associated with Nephrotic Syndrome

Elevated levels of cholesterol	Elevated levels of the enzyme PCSK9
Elevated levels of triglycerides	Decreased hepatic lipase activity
Elevated levels of VLDL, LDL, Lp(a)	Decreased HDL2 fraction (cardioprotective)

HDL- High-Density lipoprotein; LDL- Low-Density lipoprotein; Lp(a)- Lipoprotein(a); PCSK9- Proprotein convertase subtilisin/kexin type 9.

Table Va. Clinical Efficacy of Lipoprotein Apheresis in Idiopathic Nephrotic Syndrome

		Muso et al. 2014; [81;82]		Muso et al. 2001; [83]		Stenvinkel et al. [84]		Muso et al. 1994 [85]	
Study design		Prospective		Study group: Prospective LA + full-dose Steroids Control group: Retrospective full-dose steroids monotherapy		Prospective		Retrospective	
LA technique		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption	
Device		Liposorber® LA-15		Liposorber® LA-15		Liposorber® LA-15		Liposorber® LA-15	
Definition of Resistance/Refractory NS used		NS despite full-dose steroid or CyA therapy of 1M		NS despite full-dose Steroid therapy for 1M		NS for at least 6M		NS treated with full-dose steroid therapy ranging from 14d to 21M	
No. of cases/ control cases (treatment episodes)		44 (47)		17/10 (17/10)		7 (7)		8 (9)	
Primary disease (no. of cases/control group)		FSGS (23) MN (4) MCD (2) Other (15)		FSGS (14/9) MN (3/1)		MN (4) MCD (2) Other (1)		FSGS (6) MN (1) MCD (1)	
Age (mean ± SD) (years)		55.4 ± 17.3		44 ± 18/ 35 ± 20		44 ± 7		32 ± 13	
Number of LA sessions		Total: 9.6 on average		2/w x 3 1/w x 6 Total: 12 in 9w		2/w x 3 1/w x 7 Total: 13 in 10w		Maximum of 13 over a period of 4-210d*	
Concomitant treatment (no. of cases/control group)		CyA (24) Steroid pulse therapy (4)		LLD (14/2) Full-dose steroid in both groups		Non were on immunosuppressive or LLD		Base steroid therapy in all patient and LLD in 6 episodes.	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pre/ Post-treatment values a)cases b)control	**UP, g/day (24-h urine)**	6.28 ± 2.96	3.46 ± 3.34 **(p<0.01)**	a) 6.2 ± 3.3 b) 8.7 ± 4.0	a) 2.7 ± 2.7 **(p<0.01)** b) 8.2 ± 7.7 (p=0.85)	8.0 ± 2.2	5.5 ± 1.7	9.56 ± 4.03	6.21 ± 8.56 **p(<0.01)**
	ALB, g/dL	2.15 ± 0.63	2.63 ± 0.63 **(p<0.01)**	a) 2.7 ± 0.7 b) 2.8 ± 0.7	a) 3.1 ± 0.7 **(p<0.01)** b) 2.9 ± 0.1 (p=0.822)	2.0 ± 0.2	2.4 ± 0.2 **p(<0.01)**	2.23 ± 0.32	3.06 ± 0.73 **p(<0.05)**
	Cr, mg/dL or GFR (mL/min)	1.82 ± 1.60	1.62 ± 1.57	a) 1.3 ± 0.6 b) 2.1 ± 2.0	a) 0.9 ± 0.6 (p=0.161) b) 1.7 ± 2.0 (p=0.461)	72 ± 9	64	73.8 ± 30.9	82.6 ± 39
	TC, mg/dL	331.10 ± 113.25	210.38 ± 77.42 **(p<0.01)**	a) 337 ± 118 b) 448 ± 106	a) 242 ± 45 **(p<0.01)** b) 366 ± 159 (p=0.1688)	471.8 ± 85	363 ± 61.87	508.9 ±135	210.2 ± 76.6

Table Vb. Clinical Efficacy of Lipoprotein Apheresis in Idiopathic Nephrotic Syndrome, continuation

	Muso et al. 2014 [81;82]	Muso et al. 2001 [83]			Stenvinkel et al. [84]	Muso et al. 1994 [85]
Immediate post treatment outcome a)cases b)control	Very effective 10 (21.3%) Effective 15 (31.9%) Non-effective 22 (46.8%)	CRe a) 8 (47%) b) 2 (20%)	IRe a) 4 (24%) b) 1 (10%)	NS a) 5 (29%) b) 7 (70%)	Small increase in serum albumin, 6/7 patietns responded	CRe-5 (56%) IRe-1 (11%) NE-3 (33%)
Long-term outcome	2 years	2 years			1 year- in 5/6 responders	ND
	CR-11 (25%) Type I IR-10 (22.7%) Type II IR-11 (25%) NE-12 (27.3%)	CR or type I IR a) 13 (76%) b) 2 (22%)	Type II IR a) 2 (11%) b) 2 (22%)	NE a) 2 (11%) b) 5 (55%)	Serum albumin increased from 2.0 ± 2 to 3.1 ± 3	ND
Efficacy rate (relieve of nephrotic range)	72.7%	87% vs 44%			LA provides immediate and long-term serum albumin increase	66.7%

ALB-Albumin; CyA-Cyclosporine A; CR-Complete remission; Cr-Serum creatinine; CRe-Complete relief; d-Days; FSGS-Focal segmental glomerulosclerosis; GFR-Glomerular filtration rate; IR-Incomplete remission; IRe-Incomplete relief; LA-Lipoprotein apheresis; LLD-Lipid lowering drugs; M-Months; MCD-Minimal change disease; MN-Membranous nephropathy; ND-No data; NE-No-effect; NS-Nephrotic syndrome; n.s-Not significative; R-Remission; SD-Standard deviation; TC-Total cholesterol; UP-Urinary protein.
Full-dose Steroid therapy: 1 mg/kg/day.[81-83;85]
***** LA was stopped when urinary protein was reduced to less than 3.5 g/day or when more than a 50% reduction was obtained continuously for 1 week.[85]

Definitions

Muso et al. :

Complete remission (undetectable UP). [81-83]
Incomplete remission type I (UP<1.0g/day); *type II* (UP:[1.0;3.5[g/day). [81-83]
No effect (≥3.5 g/day).[81-83]

Very effective, the UP level before LA was ≥3.5 g/day and was reduced to <1.0 g/day after LA.[81]

*Effective***,** the UP level before LA was ≥3.5 g/day and was reduced to <3.5 g/day (but ≥1.0 g/day) after LA, or the UP level before LA was <3.5 g/day (but ≥1.0 g/ day) and was reduced to <1.0 g/day after LA.[81]

Noneffective, cases other than those in which LA was judged to be very effective or effective.[81]

Complete relief from NS state, UP <3.5 g/day and ALB >3.0 g/dL;[83;85]
Incomplete relief from NS state, UP <3.5 g/day but ALB <3.0 g/dL;[83;85]
*No effect***,** UP >3.5 g/day and ALB <3.0 g/dL.[83;85]

Table VI. Clinical Efficacy of Lipoprotein Apheresis in Idiopathic Focal Segmental Glomerulosclerosis

		Muso et al. [86]		Hattori et al. [87]		Raina et al. [88]	
Study design		Prospective		Retrospective		Prospective	
LA technique		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption	
Device		Liposorber® LA-15		Liposorber® LA-15		Liposorber® LA-15	
Definition of Resistance/Refractory NS used		NS despite more than 1M use of full-dose steroids and/or CyA		NS despite 8w of prednisone at 2 mg/kg/day + conventional therapy with CyA		NS despite more than 8w of treatment with steroids and/or CyA	
No. of cases/ treatment episodes (control group)		41		11/11		11	
Age (mean ± SD) (years)		43.0 ± 19.6		10.9 ± 2.7		≤21 maximum number in age group 12-14	
Number of LA sessions		8.3 ± 2.9		2/w x 3 1/ x 6 Total: 12 in 9w		2/w x 3 1/ x 6 Total: 12 in 9w	
Concomitant treatment (no. of cases/control group)		Steroid (35) CyA (8) Other ISD (8) Statins (24)		PSL 1 mg/kg/day during the 2nd course		Most were on ISD at enrolment-no initiation, discontinuation or routine changes in dosages of ISD for 2w before and 1M after treatment.	
		Pre	Post	Pre	Post	Pre	Post
Pre/ Post-treatment values a)cases b)control	**UP, g/day (24-h urine)**	ND	ND	ND	⬆ **p(<0.01)**	9.7 ± 2.5 g/m^2/d	ND
	Serum ALB, g/dL	ND	ND	ND	⬆ **p(<0.01)**	1.9 ± 0.3	ND
	Cr, mg/dL or GFR (mL/min)	ND	ND	ND	ND	ND	ND
	TC, mg/dL	ND	ND	ND	ND	507 ± 87	250 ± 75
Immediate post treatment outcome (months)		ND		CR-5 (45%) PR-2 (18%) NS-4 (37%)		0m-11 patients PR-9% (1) NS-91% (10)	
Long-term outcome		2 years-29 patients		4.7 ± 3.7 years		6M -6 patients	
		CR-12 (41%) Type I IR-6 (21%) Type II IR-8 (28%) NE-3 (10%)		CR-5 (45,5%) PR-1 (9%) NE-5 (45,5%)		CR-1 (17%) PR-3 (50%) NE-3 (33%)	
		5 years-15 patiens				12M-5 patients	
		CR-8 (53%) Type I IR-5 (33%) Type II IR-1 (7%) NE-1 (7%)				CR-40% (2) PR-20% (1) NE-40% (2)	
Efficacy rate (Nephrotic range relieve)		90%-2 years 93%-5 years		54.5%		6M-66% 12M-60%	

ALB-Albumin; CyA-Cyclosporine A; CR-Complete remission; Cr-Serum creatinine; CRe-Complete relief; GFR-Glomerular filtration rate; ISD-Immunosuppressive drugs; IR-Incomplete remission; IRe-Incomplete relief; LA-Lipoprotein apheresis; LLD-Lipid lowering drugs; M-Months; MCD-Minimal change disease; ND-No data; NE-No effect; NS-Nephrotic syndrome; Post-Post-treatment; Pre-Pre-treatment; PSL-Prednisolone; SD-Standard deviation; TC-Total cholesterol; UP-Urinary protein; W-weeks.
Full-dose Steroid therapy: 1 mg/kg/day.[86]

Definitions

Muso et al. :

Complete remission (undetectable UP).[86]
Incomplete remission type I (UP<1.0g/day); *type II* (UP:[1.0;3.5[g/day). [86]
No effect (≥3.5 g/day).[86]

Hattori et al. :

Complete remission, reduction in UP levels to less than 4 mg/m2/h for 3 consecutive days, with normal serum albumin and cholesterol levels.[87]

Partial remission, reduction in UP levels, but persistent nonnephrotic proteinuria (protein 40 mg/m2/h) in the absence of hypoalbuminemia.[87]

No effect, failure to achieve complete or partial remission.[87]

Raina et al. :

Complete remission, UP levels ≤0.2 g/g.[88]

Partial remission, UP levels of 0.2-2 g/day or decrease in UP levels ≥50% of initial screening value.[88]

Table VII. Clinical Efficacy of Lipoprotein Apheresis in Idiopathic Focal Segmental Glomerulosclerosis- Case Reports

		Miyazono et al. [89]			Yokoyama et al. [90]		Kawasaki et al. [91]		Oto et al. [92]		Hattori et al.[93]	
Study design		Case Report			Case Report		Case Report		Case Report		Case report	
LA technique		Dextran sulfate cellulose columna absorption			Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption		Dextran sulfate cellulose column absorption	
Device		Liposorber® LA-15			Liposorber® LA-15		Liposorber® LA-15		Liposorber® LA-15		Liposorber® LA-15	
Age		72			25		13		8		15	
Previous treatment		PSL 60 mg/day + mPSL 500 mg/day x3 + CyA 150 mg/day			None		PSL 60 mg + mPSL 1 g/day x3 + CyA 200 mg/day -8w		PSL 2 mg/kg/day + mPL 800 mg/day x 3- 9w CyA during 8thw		PSL 80mg/day-4w mPSL 1 g/day + PSL 60 mg/day- 4w CF 100 mg/day-12w	
Number of LA sessions		1ºT Jan 01 3/w x 2	2ºT Dec 01 3/w x 2		2/w x 3 Total: 6 during 3w		1/w x 12 1/2w x 6 1/4w x 6 Total: 24 during 12M		5x during 3w		1ºT Nov 1990 2/w x 3	2ºT Nov 1991 2/w x 2
		Total: 12									Total: 10	
Concomitant treatment (continued duration after treatment)		1ºT PSL 7.5 mg + CyA 75 mg	2ºT PSL 20 mg + CyA 150 mg		None		Low dose mPSL PVT (20 mg)		mPSL 5 mg/day + CyA 65 mg/day + PSL 800 mg/day x 3 after completion of LA therapy.		1ºT PVT 20 mg/day (10M) + CyA 100 mg/day (3M)	2ºT PSL 60 mg/day
		Pre		Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pre/ Post-treatment values a)cases b)control	**UP, g/day (24h urine)**	1ºT	7.6	1.1	5.31	0.87	8.3	ND	2-4	0.6	1ºT 18-25	<15
		2ºT	6.5	0.8							2ºT 30-35	1-3
	Serum ALB, g/dL Or Total Protein (g/dL)	1ºT	TP: 3.6	TP: 4.2	ND	ND	Serum ALB: 2.2 TP: 4.3	ND	Serum ALB: 2.5 TP: 5.1	ND	1ºT ND	ND
		2ºT	TP: 3.6	TP: 5.4							2ºT ND	ND
	Cr, mg/dL or GFR (mL/min)	1ºT	2.8	1.0	ND	ND	0.4	ND	ND	ND	1ºT 2.8	ND
		2ºT	2.9	1.1							2ºT 2.9	ND
	TC, mg/dL	1ºT	ND	214	3000	220	635	ND	399	ND	1ºT 472-678	ND
		2ºT	388	211							2ºT 350-400	ND
Outcome		After 1ºT the patient remained in PR for 11M. After 2ºT the patient was still In CR after 9M.			After 6M follow-up patient remained at PR		Patient had no proteinuria for 12 years after LA		At 6M follow-up patient proteinuria remained at 0.6 g/dL		Slight decrease in proteinuria after first treatment. Improvement in proteinuria (1–3 g/day) and renal functions during 2nd episode of NS	

ALB-Albumin; CyA-Cyclosporine A; Cr-Serum creatinine; CF-Cyclophosphamide; CR-Complete remission; GFR-Glomerular filtration rate; LA-Lipoprotein apheresis; M-Months; mPSL-Methylprednisolone; ND-No data; Nov-November; NS-Nephrotic syndrome; Post-Post-treatment; PR-Partial remission; Pre-Pre-treatment; PSL-Prednisolone; PVT-Pravastatin; T-Treatment; TC-Total cholesterol; TP-Total Proteins; UP-Urinary protein; W-Weeks.

XI. Figures

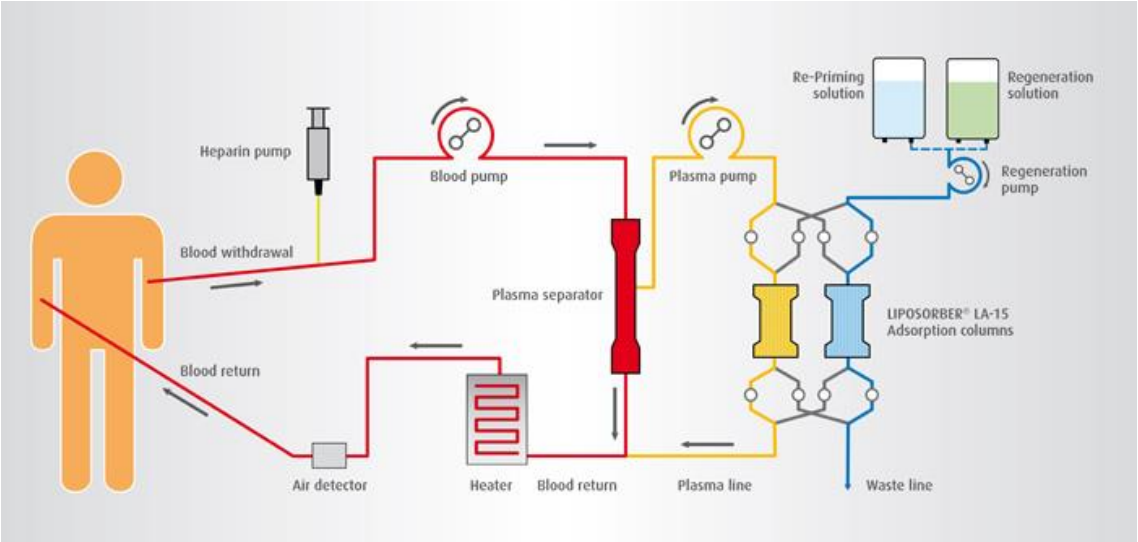

Figure 1. Schematics of Liposorber® LA-15 System; adapted from Kaneca Pharma Europe NV.

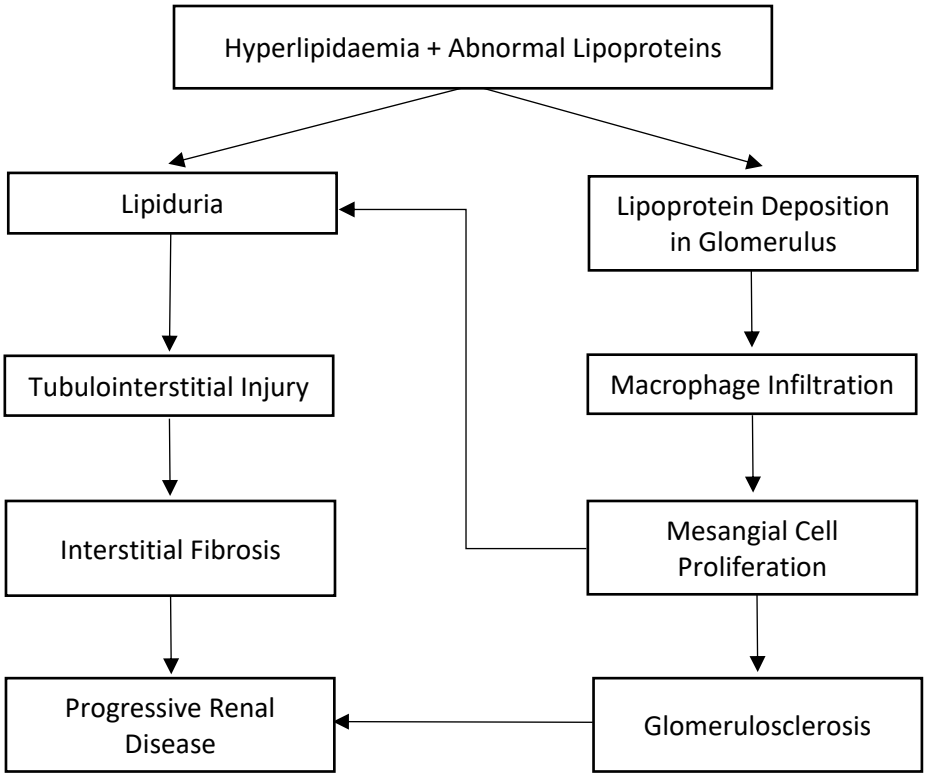

Figure 2. Simplified Physiopathology of Lipid Nephrotoxicity Hypothesis. Adapted from Muso E. (2014). Beneficial effect of LDL-apheresis in refractory nephrotic syndrome. *Clinical and experimental nephrology*, *18*(2), 286–290.

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