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journal or publication title	Clinical and Experimental Nephrology
volume	11
number	2
page range	122-127
year	2007-06-01
URL	http://hdl.handle.net/2297/29520

doi: 10.1007/s10157-007-0462-y

Advances in apheresis therapy for glomerular diseases.

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Short title: Apheresis in glomerular diseases

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Abstract
This article overviewed the immunomodulation effects and clinical evidence of apheresis in renal diseases, especially primary and secondary glomerulonephritis. A considerable permeability factor(s) derived from circulating T cells is speculated to have a crucial role in proteinuria of nephrotic syndrome (NS). Plasma exchange (PE), immunoadsorption (IAPP) using Protein A sepharose cartridges, low density lipoprotein apheresis and lymphocyte apheresis (LCAP) were tried to remove such factors or pathogenic T cells. Other glomerular diseases induced by specific antibodies such as anti-glomerular basement membrane antibodies, anti-neutrophil cytoplasmic antibodies and immune-complexes were also treated with PE, double filtration plasma apheresis, IAPP and LCAP. The recommendations based on the evidence from recent randomized controlled studies have been established in apheresis therapy for the treatment of various glomerular diseases.

Key words: apheresis, immunomodulation, glomerulonephritis, and nephrotic syndrome

1. Introduction

Therapeutic application of apheresis therapy to a wide range of glomerular disorders occurred with the development of efficient plasma cell separation and following reports of the beneficial effect in anti-glomerular basement membrane (GBM) diseases since 1975 [1]. Since then new extracorporeal techniques such as immunoadsorption (IAPP), double filtration plasma apheresis (DFPP), low density lipoprotein (LDL) apheresis and lymphocyte or granulocyte apheresis (LCAP or GCAP) developed [2], apheresis therapies have been tried to remove pathological factors in nephritic syndrome such as anti-neutrophil cytoplasmic antibodies (ANCA) mediated vasculitis, and immune-complex diseases such as lupus nephritis to remove autoantibodies, immune-complexes, or pathological lymphocytes.

In addition, glomerular permeability factor(s) derived from T cells may play a crucial role(s) in the protein excretion of nephrotic syndrome, especially minimal change nephrotic syndrome (MCNS) [3]. Circulating glomerular albumin permeability factor(s) were also detected in patients with native (primary) focal segmental glomerulosclerosis (FSGS) and recurrent FSGS after renal transplantation [4-5]. In such cases, plasma protein adsorption using Protein A sepharose cartridges [6-7] or anti-human immunoglobulin affinity immunoadsorption [7-8], plasma exchange (PE) [9-10], LDL apheresis [11] and/or LCAP [12] have been reported to be effective even for steroid-cyclosporin-A (CyA) resistant cases through removing the glomerular permeability factor(s) in some of these nephrotic patients.

In this review, we overviewed the immunomodulation effects and clinical evidence of apheresis in various glomerular diseases, especially nephrotic syndrome and severe nephritic syndrome.

2. Immunomodality of apheresis in glomerular diseases: Possible mechanisms

The exact mechanisms by which apheresis is of benefit for glomerular diseases still remain investigated, however. Possible actions of apheresis for renal diseases were summarized in Table 1. In addition to removal of pathological agents such as antibodies, immune-complexes and/or immune-associated cells, removal of pro-inflammatory mediators including cytokines, chemokines and complements, and a demonstrated improvement of immune systems including reticuloendothelial function and Th1/Th2 balance of helper T cells have been postulated to contribute to the beneficial effects of apheresis [13-14]. In addition, infusion of normal plasma may itself have beneficial effects in some diseases such as thrombotic thrombocytopenic purpura (TTP) in which replacement of a deficient plasma may be the principal mechanism of PE independent of removal of circulating factors defined as anti-von Willebrand cleaving protease (ADAMTS-13) antibodies [14].

3. Apheresis techniques for renal diseases

The most important point is to select the appropriate methods for treating patients when we do extracorporeal immunomodulation for glomerular diseases. The current technical aspects of apheresis are shown in Table 2. In brief, soluble components were treated by standard (whole) PE, fractionated PE such as DFPP using plasma separator and fractionator, cryofiltration, and plasma adsorption that utilizes either protein A, dextran sulfate, tryptophan or phenylalanine as a ligand. As for cellular components, centrifugation and specific adsorption cartridges are applied to separate lymphocytes and/or granulocytes with activated platelets.

4. Plasma exchange, DFPP and IAPP for soluble factors in glomerular diseases

1) Anti-GBM disease

The pathogenicity of anti-GBM antibodies towards the non-collagenous domain in C-terminus of the alpha 3 and/or 5 chain of type IV collagen that present in kidney and lung basement membrane. Anti-GBM disease typically presents crescentic glomerulonephritis alone or with lung hemorrhage (Goodpasture's syndrome). The titer of circulating anti-GBM antibodies, which have been detected in more than 90% of patients, correlates disease activity. Then, autoantibody removal by apheresis should be effective in concomitant with the suppression of antibody synthesis by immunosuppressive drugs. Since the initial dramatic improvement in the PE-treated patients has been reported from Hammer-Smith Hospital in 1975, it has been accepted the efficacy of PE for anti-GBM disease. However, only 2 controlled studies evaluated the efficacy of PE as an adjunct to conventional therapy. Johnson et al. [15] compared the influence of PE with 4L every 3 days plus conventional immunosuppressive therapy (prednisolone and cyclophosphamide) to immunosuppression alone in a randomized controlled trial of 17 patients with anti-GBM nephritis. They found a more rapid disappearance of circulating anti-GBM antibodies and a favorable renal function at the end of the study in the patients treated with PE (serum creatinine levels 4.4+/-0.6 mg/dL in combined therapy vs. 9.5+/-0.7 mg/dL in immunosuppression alone; $p<0.05$). In addition, the results of more than 250 patients in uncontrolled studies, published over the past 3 decades, also suggested a favorable renal outcome in about 40% of patients. Despite an effective apheresis, oligonuric patients and those on hemodialysis before apheresis rarely improve. In such cases, apheresis was proposed only if lung hemorrhage was present. Current strategy for anti-GBM disease is to do apheresis such as PE or DFPP in all patients dialysis independent before therapy and those with lung complication even on end-stage renal failure.

2) ANCA related diseases

The mechanisms by which apheresis is of benefit for small-vessel vasculitides remain obscure , however [16]. Recent studies revealed that ANCA itself could induce necrotizing glomerulonephritis in animal model, and that Th1 type helper T cell induced IgG subclasses, IgG1 or IgG1/IgG3 may relate the disease activity of ANCA-related vasculitis. Hence, it seems reasonable to remove the circulating ANCA and to alter the Th1/Th2 type helper T cell balance by extracorporeal immunomodulation therapy in ANCA-related diseases. The effectiveness of PE has been reported in some patients with rapidly progressive glomerulonephritis (RPGN), in which ANCA-associated vasculitis is the most common cause. In 6 randomized controlled trials [17-22], there was no statistically significant benefit from plasma exchange in a whole group, however. The significant difference was reported in the dialysis-dependent group with RPGN and systemic involvement, in which 10 out of 11 patients treated by PE and 3 of 8 control patients recovered renal function by 4 weeks in previous studies. In addition, good outcomes after PE have been reported in patients with lung hemorrhage and severe neurological diseases. In this notion, the multi-center European MEPEX trial (methylprednisolone pulse therapy versus PE as additional therapy for severe ANCA associated glomerulonephritis) had been attempted to define the role of PE in patients with ANCA related vasculitis and an initial creatinine level of more than 500 μmol/L. In this study,

PE was a positive predictor of dialysis independence after 12 mo for the entire patient group. PE remained a positive predictor when patients who were dialysis dependent at presentation were analyzed separately [22]. These results supporting a beneficial role of apheresis in whole small-vessel vasculitides is still small, but dialysis-dependent patients are the group who may have a benefit by PE in the presence of severe systemic diseases or high risks for complications such as infection.

3) Lupus nephritis

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which commonly involves glomerular disorders. The prognosis of patients with lupus glomerulonephritis, especially proliferative glomerulonephritis the World Health Organization (WHO) class IV or ISN/RPS 2003 class IV-G and IV-S, is poor, despite treatment with immunosuppressive therapy in combination with glucocorticoids and cytotoxic drugs such as cyclophosphamide. Autoantibodies to double-stranded (ds)-DNA and other nuclear components are thought to participate in the initiation and progression of lupus nephritis. Renal injury may result from either deposition or in situ formation of immune-complexes or direct injury of pathogenic autoantibodies or cytotoxic infiltrated cells such as macrophages and T cells. In this notion, the use of apheresis therapy as more specific treatments to remove pathologically relevant autoantibodies or circulating cells seems rational [23].

Various apheresis techniques such as PE, DFPP, adsorption apheresis using either protein A, dextran sulfate, tryptophan or phenylalanine as a ligand, have been explored for treatment of lupus nephritis [23]. Plasmapheresis therapy has been used, but there have been few controlled clinical observations of its efficacy. In 1992, Lewis and the lupus nephritis collaborative study group [24] carried out a randomized, controlled trial comparing a standard-therapy regimen of prednisone and cyclophosphamide (standard therapy) with a regimen of standard therapy plus plasmapheresis in 86 patients with severe lupus nephritis in 14 medical centers. The patients underwent PE 3 times weekly for 4 weeks. As a result, 46 patients received standard therapy, and 40 patients received standard therapy plus plasmapheresis. Patients treated with PE had a significantly more rapid reduction of serum concentrations of antibodies against ds-DNA and cryoglobulins, however. Treatment with PE plus a standard therapy does not improve the clinical outcome in patients with SLE and severe nephritis, as compared with the standard therapy alone. In addition, Wallace and collaboration group [25] were tried to access the efficacy of randomized controlled trial of methylprednisolone pulse therapy with synchronization cyclophosphamide or apheresis for proliferative lupus nephritis. Eighteen patients with WHO Class III or IV renal biopsies and chronicity indices less than 6 points were prospectively randomized to receive 6 courses of parenteral cyclophosphamide over 8 months along with prednisone. No intergroup comparisons were significant. Then, this study concluded that the addition of synchronization apheresis to cyclophosphamide therapy does not improve the course of patients with proliferative lupus nephritis. Other trials using adsorption apheresis showed the reduction of autoantibody titers and proteinuria, but these data on patients with lupus nephritis are limited. Although apheresis therapy could modify the underlying pathogenic mechanisms, PE or other apheresis therapy offers no clear clinical benefit over conventional immunosuppressive therapy in severe proliferative lupus nephritis on the basis of currently available evidence. However, apheresis therapy seems promising in

individual patients with acute life-threatening diseases such as catastrophic anti-phospholipid syndrome (CAPS) or who resistant to standard drug therapy, because of a rapid removal of circulating pathological factors.

4) Nephrotic syndrome

Proteinuria in patients with MCNS and FSGS is speculated to be caused by damage to the negative charge barrier of the glomerular capillary walls by some cationic substance [26]. Certain substances derived from serum, urine or lymphocytes of patients with MCNS have been reported as being responsible for the damage [3]. In addition, abnormal T cell function was also proposed as a pathogenic factor [27-28]. Savin's group reported that plasmapheresis could diminish proteinuria and stabilize renal function in a part of patients with steroid-resistant idiopathic FSGS, suggesting that FSGS have some different local or systemic factor(s) unrelated to glomerular permeability [9-10, 28]. In addition, a recent prospective trial in 10 patients at high-risk for FSGS recurrence because of rapid progression to renal failure (n = 4) or prior transplant recurrence of FSGS (n = 6) underwent a course of 8 PE treatments in the peri-operative period. Seven patients, including all 4 with first grafts and 3 of 6 with prior recurrence, were free of recurrence at follow-up (238-1258 days) [29].

Dantal et al. reported the active factor binds to protein A in FSGS, which was speculated as immunoglobulins, immunoglobulin fragments or proteins binding to Fc chains such as complement components, transforming growth factor-β or other Ig-binding proteins [6, 8]. Bosch and Wendler [30] summarized recent studies provide evidence that patients with recurrent FSGS after renal transplantation and those of primary FSGS can profit from PE or immunoadsorption. They concluded that the indication of performing extracorporeal plasma therapy for recurrent FSGS would at best fall into Category II (accepted supportive therapy) according to the guidelines of the American Society for Apheresis, but for primary FSGS rather than into Category III (conflicting results, anecdotal reports).

Hyperlipidemia, especially LDL, is an important factor for the outcome of steroid resistant nephrotic syndrome. Muso et al. [11] firstly reported the effect of LDL apheresis in steroid-resistant nephrotic syndrome, 6 patients with FSGS, one with MCNS, and one with membranous nephropathy (MN) and FSGS. The LDL apheresis, carried out 2-13 times (mean 7.3) for one nephrotic episode and combined with steroid pulse therapy, led to rapid amelioration of hyperlipidemia. Moreover, more than 50% reduction of proteinuria occurred (less than 3.5 g/day) in 6 nephrotic episodes (5 patients). A significant elevation of serum albumin (more than 3.0 g/dl) was also obtained in five of these episodes. In addition, Yokoyama et al. [31] found that LDL apheresis improved the response to steroid therapy in the patients of FSGS associated with nephrotic syndrome resistant to steroid, and that only electron microscopy was able to detect histological recovery in the patients who showed a decrease of proteinuria after LDL apheresis. They also reported a case with primary FSGS in whom a complete remission of nephrotic state was achieved with LDL apheresis alone [32]. In the only prospective study reported by Stenvinkel and Swedish group in 2000 [33], LDL apheresis caused a rapid 30-40% decrease in serum cholesterol and plasma Lp (a) levels in patients with nephrotic syndrome. Their prospective study also suggested that short-term LDL apheresis might increase serum albumin levels in nephrotic patients. Although the level of evidence is still low, it is expected that a rapid improvement of hypercholesterolemia by LDL

apheresis will provide more rapid relief from nephrotic state than immunosuppressive therapy alone in steroid-resistant nephrotic syndrome, especially primary FSGS.

5. LCAP or GCAP for glomerular diseases, nephrotic syndrome and vasculitis

In general, macrophages, cytotoxic and Th1 type helper T cells play a central role in the glomerular injury of crescentic glomerulonephritis. In addition, glomerular permeability factor(s) derived from T cells may play a crucial role(s) in the protein excretion of nephrotic syndrome, especially MCNS and FSGS [3]. It has been reported that the removal of these pathogenic cells by lymphocytapheresis is effective in the treatment of autoimmune diseases or lymphocyte abnormalities, such as rheumatoid arthritis [34].

1) Nephrotic syndrome

After LCAP in nephrotic syndrome, the total number and population of peripheral blood WBC and CD4/CD8 ratio did not change, however, total number of lymphocytes, T cells, B cells and HLA-DR positive activated T cells decreased significantly in the response group. The alteration of lymphocyte subsets was not found in the non-response group after LCAP. No adverse effects were recorded during or after LCAP in any patients. Proteinuria tended to decrease at 2 weeks post-treatment (8.2±1.8g/day before and 5.6±1.3 g/day at 2 weeks). Especially, patients with MCNS or FSGS showed good response to LCAP resulting in dramatic decrease of daily proteinuria. Urinary protein/creatinine ratio also decreased between –30% and –94% in these cases. Finally, complete or partial remission (proteinuria <1.0 g/day) was seen in patients treated by LCAP and following immunosuppressive or supportive therapy. In the results of LCAP [12], the serum levels of immunoglobulins, complements or lipids only changed in a small part even in the response group, suggesting that the mechanism of LCAP may be different from those of plasma protein adsorption using Protein A sepharose cartridges [6-7], anti-human immunoglobulin affinity immunadsorption [7-8], or LDL apheresis [11] as previously described. However, impaired size barrier of the glomerular capillary walls causing the increased glomerular protein permeability could not be improved by LCAP [12].

2) Crescentic glomerulonephritis with ANCA-associated vasculitis or IgA nephropathy

Furuta et al. [35] investigated the efficacy of LCAP for treatment of RPGN, in comparison with steroid-pulse treatment. They enrolled 24 patients with RPGN proven by biopsy in a prospective randomized study. The 12 in the LCAP group completed 9 LCAP sessions of 3 consecutive weeks, with a Cellsorba cartridge (CS-120). The other 12 controls received 1 g of methylprednisolone for 3 consecutive days in each of 3 consecutive weeks. All patients received prednisolone (20 mg/day) and cyclophosphamide (50 mg/day). The patients in LCAP group were 7 with IgA nephropathy and 5 with pauci-immune; and for 5 and 7 of those in the steroid-pulse group, respectively. The LCAP group showed significant improvements in renal function and proteinuria. The ratio of CD4 to CD8 cells before and after the treatment showed no significant change in the lymphocytapheresis group, but the CD14/3 ratio substantially lower, suggesting this maneuver removed mainly CD8 and CD14 cells. They concluded that LCAP is more effective than steroid-pulse treatment for reduction of glomerular injury due to RPGN, as an effect of its selective removal of CD8 and CD14 cells. In addition, Hasegawa et al [36] also reported the efficacy of cytapheresis for the treatment of RPGN caused by

myeloperoxidase (MPO)-ANCA-associated vasculitis, in comparison between a cytapheresis group and a steroid pulse group. In their study, the cytapheresis group included 10 patients who were treated by GCAP with the Adacolumn in 5 patients and other 5 patients by LCAP with the Cellsorba. In the cytapheresis group, the mortality rate by infection could be reduced at 1 year after treatment.

6. Conclusions

In aspect of immunomodulation, apheresis therapies not only accelerate the disappearance of circulating pathogenic factors such as autoantibodies, circulating permeability factor(s) and T cells, but also be able to modulate the immune response in backgrounds of glomerular diseases. It seems reasonable to conclude that removal of the circulating pathogenic factors by apheresis is an effective adjunct to conventional therapy in severe glomerular diseases. In future, prospective randomized trials with a proper statistical evaluation will define the exact effects of apheresis in the outcome of each glomerular disease.

References

1) Lockwood CM, Boulton JJ, Lowenthal RM, Simpson IJ, Peters DK. Recovery from Goodpasture's syndrome after immunosuppressive treatment and plasmapheresis. Br Med J 1975; 2:252-254.

2) Agishi T. Birth of the concept and the development of extracorporeal immunomodulation. Ther Apher 2002;6:312-316.

3) Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M. A glomerular permeability factor produced by human T cell hybridomas. Kidney Int 1991;40:453-460.

4) Godfrin Y, Dantal J, Bouhours JF, Heslan JM, Soulillou JP. A new method of measuring albumin permeability in isolated glomeruli. Kidney Int 1996;50:1352-1357.

5) Savin VJ, Sharma R, Sharma M, McCarthy ET, Swan SK, Ellis E, Lovell H, Warady B, Gunwar S, Chonko AM, Artero M, Vincenti F. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. N Engl J Med 1996;334:878-883.

6) Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jacques Y, Ligny BH, Niaudet P, Charpentier B, Soulillou JP. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med 1994;330:7-14.

7) Haas M, Godfrin Y, Oberbauer R, Yilmaz N, Borchhardt K, Regele H, Druml W, Derfler K, Mayer G. Plasma immunadsorption treatment in patients with primary focal and segmental glomerulosclerosis. Nephrol Dial Transplant 1998;13:2013-2016.

8) Dantal J, Godfrin Y, Koll R, Perretto S, Naulet J, Bouhours JF, Soulillou JP. Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol 1998;9:1709-1715.

9) Artero ML, Sharma R, Savin VJ, Vincenti F. Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in patients with recurrent focal glomerulosclerosis. Am J Kidney Dis 1994;23:574-581.

10) Feld SM, Figueroa, Savin V, Nast CC, Sharma R, Sharma M, Hirschberg R, Adler SG. Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis in

native kidneys. Am J Kidney Dis 1998;32: 230-237.
11) Muso E, Yashiro M, Matsushima M, Yoshida H, Sawanishi K, Sasayama S. Does LDL-apheresis in steroid-resistant nephrotic syndrome affect prognosis? Nephrol Dial Transplant 1994;9:257-264.
12) Yokoyama H, Shimizu M, Wada T, Yoshimoto K, Iwata Y, Shimizu K, Sakai N, Furuichi F, Hisada Y, Takakuwa H, Kobayashi K. The beneficial effects of lymphocytapheresis for treatment of nephrotic syndrome. Ther Apher 2002;6:167-173.
13) Yagishita A, Kikuchi K. Apheresis of immune diseases and apheresis using immunological specificity. Ther Apher 2002;6:358-364.
14) Madore F, Lazarus JM, Brady H. Therapeutic plasma exchange in renal diseases. J Am Soc Nephrol 1996;7:367-386.
15) Johnson JP, Moore JJ, Austin HB, Balow JE, Antnovych TT, Wilson CB. Therapy of anti-glomerular basement membrane antibody disease: Analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine (Baltimore) 1985;64:219-227.
16) Gaskin G, Pusey CD. Plasmapheresis in antineutrophil cytoplasmic antibody-associated systemic vasculitis. Ther Apher 2001;5:176-181.
17) Glöckner WM, Sieberth HG, Wichmann HE, Backes E, Bambauer R, Boesken WH, Böhle A, Daul A, Graben N, Keller F, Klehr HU, Köhler H, Metz U, Schulz W, Thoenes W, Vlaho M. Plasma exchange and immunosuppression in rapidly progressive nephritis: a controlled, multi-center study. Clin Nephrol 1988; 29: 1-8.
18) Pusey CD, Rees AJ, Evans DJ, Petters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int 1991; 40: 757-763.
19) Rifle G, Dechelette E. Treatment of rapidly progressive glomerulonephritis by plasma exchange and methylprednisolone pulses. A prospective randomized trial of cyclophosphamide. Interium analysis. The French Cooperative Group. Prog Clin Biol Res 1990; 337: 263-267.
20) Mauri JM, Gonzales MT, Poveda R. Therapeutic plasma exchange in the treatment of rapidly progressive glomerulonephritis. Plasma Ther & Transfus Technol 1985; 6: 587-591.
21) Cole E, Cattran D, Magil A Greenwood C, Churchill D, Sutton D, Clark W, Morrin P, Posen G, Bernstain K, Dyck R, and the Canadian Apheresis Study Group. A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. Am J Kidney Dis 1992; 20:261-269.
22) de Lind van Wijngaarden RAF, Hauer HA, Wolterbeek R, Jayne DRW, Gaskin G, Rasmussen N, Noël LH, Ferrario F, Waldherr R, Hagen EC, Bruijn JA, Bajema IM, The European Vasculitis Study Group (EUVAS). Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 Ppatients with severe renal involvement. J Am Soc Nephrol 2006;17:2264-2274.
23) Mistry-Burchardi N, Schönermarck U, Samtleben W. Apheresis in lupus nephritis. Ther Apher 2001;5:161-170.
24) Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. N Engl J Med 1992;326:1373-1379.
25) Wallace DJ, Goldfinger D, Pepkowitz SH, Fichman M, Metzger AL, Schroeder JO, Euler HH. Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. J Clin Apheresis 1998;13:163-166.
26) Taube D, Brown Z, Williams DG. Impaired lymphocyte and suppressor cell function in

minimal change nephropathy, membranous nephropathy and focal glomerulosclerosis. Clin Nephrol 1984;22:176-182.
27) Yokoyama H, Kida H, Tani Y, Abe T, Tomosugi N, Koshino Y, Hattori N. Immunodynamics of minimal change nephrotic syndrome in adults T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol 1985;61:601-607.
28) Sharma M, Sharma R, McCarthy ET, Savin VJ. "The FSGS factor:" enrichment and in vivo effect of activity from focal segmental glomerulosclerosis plasma. J Am Soc Nephrol 1999;10:552-561.
29) Gohh RY, Yango AF, Morrissey PE, Monaco AP, Gautam A, Sharma M, McCarthy ET, Savin VJ. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. Am J Transplant 2005;5:2907-2912.
30) Bosch T, Wendler T. Extracorporeal plasma treatment in primary and recurrent focal segmental glomerular sclerosis: A review. Ther Apher 2001;5:155-160.
31) Yokoyama K, Sakai S, Sigematsu T, Takemoto F, Hara S, Yamada A, Kawaguchi Y, Hosoya T. LDL adsorption improves the response of focal glomerulosclerosis to corticosteroid therapy. Clin Nephrol 1998;50:1-7.
32) Yokoyama K, Sakai S, Yamaguchi Y, Suzuki Y, Hinoshita F, Hara S, Yamada A, Ogura, Kawaguchi Y, Sakai O. Complete remission of the nephrotic syndrome due to focal glomerular sclerosis achieved with low density lipoprotein adsorption alone. Nephron 1996;72:318-320.
33) Stenvinkel P, Alvestrand A, Angelin B, Eriksson M. LDL-apheresis in patients with nephrotic syndrome: effects on serum albumin and urinary albumin excretion. Eur J Clin Invest 2000;30:866-70.
34) Takenaka Y: Lymphocytapheresis. Artif Organs 1996;20:914-916.
35) Furuta T, Hotta O, Yusa N, Horigome I, Chiba S, Taguma Y: Lymphocytapheresis to treat rapidly progressive glomerulonephritis: A randomised comparison with steroid-pulse treatment. Lancet 1998;352:203-204.
36) Hasegawa M, Watanabe A, Takahashi H, Takahashi K, Kasugai M, Kawamura N, Kushimoto H, Murakami K, Tomita M, Nabeshima K, Oohashi A, Kondou F, Ooshima H, Hiki Y, Sugiyama: Treatment with cytapheresis for antineutrophil cytoplasmic antibody-associated renal vasculitis and its effect on anti-inflammatory factors. Ther Apher Dial. 2005;9:297-302.

Table 1: Possible mechanisms of apheresis in renal diseases.

#1 Removal of pathological circulationg factors, abnormal factors or physiologic factors in excess:

1) Antibodies: anti-GBM diseases, ANCA associated diseases, lupus nephritis (anti-DNA), anti-phospholipid diseases
2) Immune-complexes: lupus nephritis, cryoglobulinemia
3) Dysproteins: macroglobulinemia, myeloma, amyloid-A protein, LDL (FSGS)
4) Toxic factors: endotoxin, permeability factors? (MCNS, FGSS)
5) Activated lymphocytes: vasculitis, nephrotic syndrome (MCNS, FSGS)

#2 Replacement of deficient plasma factors:

1) Thrombotic thrombocytopenic purpura: ADAMTS-13

#3 Other effects on the immune system:

1) Removal of inflammatory mediators: cytokines/chemokines, cannabinoids
2) Improvement of reticuloendothelial system function
3) Effects of immune regulation

GBM, glomerular capillary basement membrane; ANCA, anti-neutrophil cytoplasmic antibodies; LDL, low-density lipoprotein; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome.

Table 2: Application of apheresis techniques for renal diseases

Procedure	Ligands or materials	Removed or adsorbed factors
Plasma exchange	Replacement of plasma*	Autoantibodies, CIC, dysproteins
Double filtration	Plasma fractionator	CIC, autoantibodies, dysproteins
Cryofiltration	Plasma fractionator	Cryoproteins
Plasma adsorption	Phenylalanine	Anti-DNA, CIC
	Dextran sulfate	Anti-DNA, CIC, lupus anticoagulants, LDL
	Protein A	IgG, CIC, permeability factors (?)
	Anti-IgG Fc	IgG, CIC, permeability factors (?)
Blood adsorption	Polymyxin B (Dextran sulfate)	Endotoxin, cytokines
Cytoapheresis		
LCAP**	Lymphocyte separators	Lymphocytes, activated platelets
GCAP***	Granulocyte separators	Granulocytes

*, centrifugal method or plasma separator; **, lymphocytapheresis, ***, granulocytapheresis
CIC, circulating immune-complexes; LDL, low-density lipoprotein

Table 3: Evidence on apheresis therapy in glomerular diseases.

Diseases		Methods	Study Design(N) (references, ref.)	Level of evidence	Results
Anti-GBM		PE	RCT (1) (ref.15)	2	Better renal survival with PE
RPGN		PE	RCT (6) (ref.17-22)	1-3	No benefit for entire group in 4/5 trials (80%), Discontinuation of dialysis more on PE in 3/6 trials (50%) More effective than steroid-pulse therapy in ANCA vasculitis, free from HD (19/35, 54% vs. 11/34, 32% in MEPEX trial)
		LCAP	RCT (1) (ref.35)	2	More effective than steroid-pulse therapy
Lupus nephritis		PE	RCT (5) (ref.24-25)	2-3	Early disappearance of autoantibodies No benefit for long-term clinical outcome
FSGS	Primary	PE	UCT (3) (ref.30)	5-6	Remission in 11/20 patients (55%)
		LDL-A	UCT (2) (ref.11,31)	5	Remission in 10/21 patients (48%)
		LCAP	UCT (1) (ref.27)	6	Remission in 2/3 patients (67%)
	Recurrent	PE	UCT/RHT(5) (ref.10,30)	4-6	Remission in 19/29 patients (66%)
		Protein A	UCT (3) (ref.6-7)	5	Short-term remission in 10/11 patients (91%) Long-term remission in 2/8 patients (25%)
		LCAP	Case study*	6	Remission in a renal transplanted case
	Prevention	PE	UCT(1) (ref.29)	5	No recurrence in 7/10 (70%) of high risk group

Anti-GBM, anti-glomerular basement membrane disease; RPGN, rapidly progressive glomerulonephritis; FSGS, focal segmental glomerulosclerosis; PE, plasma exchange; LCAP, lymphocytapheresis; LDL-A, low density lipoprotein apheresis; RCT, randomized controlled trial; UCT, uncontrolled trial; RHT, retrospective historical controls. *: a recent case in our center