Focal Segmental Glomerulosclerosis (FSGS) and suPAR protein

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DISCLOSURES:

The speaker has the following potential conflicts

- TerumoBCT, Inc. – Honoraria, Consulting
- Therakos, Inc. – Honoraria
- Alexion Pharmaceuticals – Advisory Board
- Aethlon Medical Inc. – Consulting

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FSGS, suPAR and selective plasmapheresis

OUTLINE:

1. Recurrence of FSGS and evidence for circulating permeability factors.
2. FSGS is common and often causes kidney failure.
3. FSGS and West African genes.
4. FSGS is a group of diseases.
5. Podocyte foot-process architecture.
6. Podocyte foot-process damage.
7. Candidate molecules: 30-50 kDa factors, CLC1, suPAR.
8. Indications for TPE in treatment of FSGS.
9. Types of plasmapheresis for FSGS.
10. Why non-selective TPE is recommended.
The Lancet · Saturday 19 August 1972

**RECURRENT OF IDIOPATHIC NEPHROTIC SYNDROME AFTER RENAL TRANSPLANTATION**

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**Summary**  
Three patients with steroid-resistant idiopathic nephrotic syndrome were studied at onset and during recurrent nephrotic syndrome after renal transplantation. Renal biopsies at the onset of the nephrotic syndrome showed typical urine does not clear of protein and these patients progress to renal failure. We have studied four such patients at the onset of their disease and after renal transplantation. The nephrotic syndrome recurred in three of them shortly after renal transplantation.

**Case-reports**

**FIRST CASE**

This boy developed intermittent periorbital oedema at 7½ years of age. 6 months later the nephrotic syndrome was diagnosed (fig. 1). Prednisone 80 mg. per day for 21 days did not decrease proteinuria. 6 weeks later anasarca was present and laboratory studies demonstrated a nephrotic syndrome (table 1). 7 months later, laboratory studies were unchanged and prednisone 60 mg. per day was given for 20 days without decrease in proteinuria. 10 months later, when renal function was decreasing, azathioprine ('Imu-

FSGS (Focal Segmental Glomerulosclerosis)

Recent case report:

- 27 year old man with end-stage renal failure (ESRD) due to primary FSGS.
- Received kidney transplant from sister (age 24).
- Day 2 post-op: recurrence of nephrotic syndrome (heavy proteinuria).
- Day 6 post-op: Kidney transplant biopsy showed recurrence of FSGS, with podocyte foot-process effacement and effusion.
- Rapid loss of renal function and severe depletion of serum albumin.
- Day 14 post-op: Kidney removed and retransplanted into a 66 year old man with ESRD (diabetic nephropathy) after ethics committee consultation.
- Immediate graft function with rapid reduction in proteinuria.
- Day 8 and day 25 after retransplantation: Kidney transplant biopsy showed glomerular lesions returning to normal.

FSGS (Focal Segmental Glomerulosclerosis)

Plasma exchange (TPE) for recurrent FSGS:

- The recurrence of FSGS after kidney transplantation has been known for four decades (1).
- FSGS recurs post-transplant in about 23% of adults (3). Rates are higher in children, or when a previous transplant has been lost to recurrence.
- Successful treatment of post-transplant recurrent FSGS by plasma exchange (TPE) is well established (4-11).
- Opinion is in favor of TPE for severe cases of pre-transplant FSGS.

(7) Zimmerman SW: Nephron 40:241-245, 1985
FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a common disease of children and young adults.

Clinical features:
- Proteinuria, microscopic hematuria, hypertension.
- Nephrotic syndrome in 30 – 50%.
- Progressive renal failure: 70% reach end stage in 10 years.

Treatment:
- 20 - 40% of nephrotic cases may be helped by corticosteroids.
- Data also support use of cyclosporine, mycophenolate, cyclophosphamide, etc.
- Use ACE-inhibitors or ARB’s (non-specific treatment for heavy proteinuria and/or progressive glomerular impairment).

Recurrence after transplant:
- Occurs in 23% or more of cases
- Responds to plasma exchange, rituximab, etc.
FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a common disease of children and young adults.

- Prominent cause of ESRD. (1)
- The incidence is increasing. (1)
- Most common cause of non-diabetic nephrotic syndrome in USA.
- Global incidence estimated at 8 cases per million per year. (2)
- Lifetime risk in USA is:
  ~0.2% for European Americans
  ~0.7% for African Americans. (3)

FSGS is more common in African Americans.

- African-American ancestry confers high risk for FSGS and hypertension-attributed ESRD (end-stage renal disease); (also of HIV-nephropathy and diabetes-associated ESRD).
- Early hypotheses included speculation regarding a one-time selection event for salt-conserving genes.
- Then genome-wide analysis (GWAS) showed association with a locus on chromosome 22, in or near the gene for MYH9 (myosin heavy chain 9). (1)
- However, causal mutations in MYH9 could not be found. (2)
- Linkage disequilibrium with a nearby site was suspected; mutations in the APOL1 gene were found. (3)

(2) Freedman BI et al., Kidney Int 75:736, 2009
Kidney Disease Is Parasite-Slaying Protein’s Downside

Kidney disease could be the price of resistance to a virulent parasite. Researchers describe two Jekyll-and-Hyde genetic variations online in Science this week (www.sciencemag.org/cgi/content/abstract/1193032) that can lead to kidney shutdown but may also fend off a microorganism that causes sleeping sickness in thousands of people in Africa.

“This is perhaps the best example, except for sickle cell anemia, of a common disease being caused by genetic variants that also play a role in resistance to infectious disease,” says human geneticist Sarah Tishkoff of the University of Pennsylvania. Similar findings may soon follow, researchers predict. The study “offers a lot of encouragement that we are going to find more cases where there are genetic bases for human adaptations,” says evolutionary biologist Gregory Wray of Duke University in Durham, North Carolina.

For a long time, the prime example of how natural selection can favor “harmful” mutations if they also confer pathogen protection has been sickle cell disease. A mutation in the gene for hemoglobin produces deformed red blood cells and can lead to an early death in severe cases. But it also enhances resistance to the most serious manifestation of malaria: Plasmodium falciparum, which also affects African people.

The researchers studied two variants of Apolipoprotein L-1 (ApoL1), the gene, which codes for the blood protein apolipoprotein L-1 (ApoL1). The researchers used data from the 1000 Genomes Project—which is sequencing DNA of people from around the world—and scoured this chromosome region for mutations that were much more common in Africans than in Europeans. Then by statistically analyzing the gene variants in African Americans who had either of the past 10,000 years. “The variants must have positive effects in order to balance out kidney disease,” Pollak says.

He and his colleagues hypothesized that the G1 and G2 versions of Apol1 better protect against Trypanosoma brucei, a microscopic parasite spread in Africa by tsetse flies. The standard version of Apol1 slays one subspecies of the parasite, T. brucei brucei, but not another subspecies, T. brucei rhodesiense, which makes a protein called SRA that neutralizes the blood defender.

But G1 and G2 reconfigure Apol1, restoring its potency. Blood plasma from people who carried G1 or G2 killed the rhodesiense version of the parasite, as did lab-made copies of the altered proteins. “The effect was really dramatic,” Pollak says.

Parasitologist Jayne Raper of New York University says the new study illustrates the ongoing “molecular arms race between host and pathogen.” However, the study isn’t conclusive, the authors and outside experts agree. The Yoruba people hail from West Africa, and the study included a small number of 10 Yoruba and 10 African American subjects. The risk for kidney disease is low in the general population. However, the authors say that 60% of Yoruba subjects showed evidence of the G1 mutation and 80% of African Americans showed evidence of the G2 mutation.

The research team is now trying to understand the mechanisms behind the kidney diseases, the team identified two alterations in the APOL1 gene that corresponded to kidney disease as well as to protection against sleeping sickness. It will be interesting to see if the altered gene leads to kidney disease in the general population.
FSGS (Focal Segmental Glomerulosclerosis)

FSGS is more common in African Americans.

Good gene, bad gene. The same gene variants that promote destruction of the kidney’s filtration units (above) also combat Trypanosoma brucei rhodesiense parasites.

Leslie M. Science 329:263, 2010 (Editorial)
FSGS (Focal Segmental Glomerulosclerosis)

**FSGS is more common in African Americans.**

- In African-Americans, FSGS and hypertension-attributed ESRD are associated with two independent sequence variants in the *APOL1* gene on chromosome 22.

- FSGS odds ratio = 10.5 (95% confidence interval 6.0-18.4); H-ESRD odds ratio = 7.3 (95% confidence interval 5.6-9.5).

- The two *APOL1* variants are common in African chromosomes but absent from European chromosomes and both reside within haplotypes that harbor signatures of positive selection. ApoL1 (apolipoprotein L-1) is a serum factor that lysed trypanosomes.

- In vitro assays revealed that only the kidney disease-associated ApoL1 variants lysed *Trypanosoma brucei rhodesiense*.

FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases.

Etiological Classification:

1. Primary ("classic", "idiopathic" or "immune") subgroup: recurs in transplants.
2. Infectious (viral) subgroup: HIV, Parvovirus B19, etc.
3. Toxic (drug-induced) subgroup: pamidronate, anabolic steroids, interferon, etc.
4. Secondary ("post-adaptive") subgroup: reduced renal mass, obesity, vesico-ureteric reflux, glomerular hyperfiltration, etc.
5. Genetic subgroup: hereditary defects of podocyte proteins.
FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases.

**Histological Classification:**

1. Classic FGS
   - also called FGS NOS (Not Otherwise Specified)
   - most common type
   - histologic diagnosis of exclusion (if none of below)
   - many recur in transplants (“idiopathic” type)
2. Collapsing variant
3. Tip variant
4. Perihilar variant
5. Cellular variant
Histological plus clinical:

- “NOS” + “tip” + “perihilar” variants
  - classic “immune” subgroup
  - circulating glomerular permeability factor
  - can recur in transplants
- “Collapsing” + “cellular” variants
  - infectious & toxic etiologies (HIV, Parvo B19, pamidronate, etc.)
- Secondary type (“Post-adaptive”)
  - hyperfiltration injury (glomerular vasodilation /overload /stress)
- Genetic types (“Hereditary podocytopathies”)
  - hereditary defects of podocyte proteins (these affect the integrity of podocyte and slit diaphragm structures).
**Histological plus clinical:**

- "NOS" + "tip" + "perihilar" variants
  - classic "immune" subgroup
  - circulating glomerular permeability factor
  - can recur in transplants
- "Collapsing" + "cellular" variants
  - infectious & toxic etiologies
- Secondary type ("Post-adaptive")
  - hyperfiltration injury
- Genetic types ("Hereditary podocytopathies")
  - hereditary defects of podocyte proteins.

What all of these have in common is damage to the podocyte foot processes of the glomerular epithelial cells.
Podocyte foot processes (of glomerular epithelial cells)

**Healthy:**
- Urinary filtrate
- Filtration slit
- Actin cytoskeleton
- Podocyte foot process
- Flow of molecules
- Glomerular capillary lumen

**Collapsed / “effaced”:**
- Urinary filtrate
- Podocyte fusion and collapse
- Reorganization of actin cytoskeleton
- Albumin
- Glomerular capillary lumen
Normal Glomerulus

- Bowman's Capsule
- Parietal Epithelium
- Visceral Epithelium (Podocyte)
- Glomerular Basement Membrane (GBM)
- Endothelium
- Capillary Lumen
- Mesangium
- Bowman's Space (Urinary Space)

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Transmission Electron Microscopy – Glomerular Capillary Loop
Podocyte foot-processes

Outside = epithelium

Inside = endothelium

Endothelial fenestrae

Scanning Electron Microscopy – Glomerular Capillary Loop

Micrograph © The McGraw-Hill Companies Inc, 2011
“Slit diaphragms” span between podocyte foot processes.

Inside = Endothelium (Fenestrated)

Outside = Epithelium (Podocytes)

Formation of glomerular filtrate
Podocyte Foot Process Architecture

“Slit diaphragms” span between podocyte foot processes

Podocyte Foot Process Architecture

“Slit diaphragms” span between podocyte foot processes

Genetic abnormalities of podocyte proteins cause FSGS-type lesions

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Gene/Protein</th>
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<tbody>
<tr>
<td>Finnish type</td>
<td>Nephrin</td>
<td></td>
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<tr>
<td>NPHS2 mutation</td>
<td>Podocin</td>
<td></td>
</tr>
<tr>
<td>Familial FSGS 1</td>
<td>α actinin 4</td>
<td></td>
</tr>
<tr>
<td>Familial FSGS 2</td>
<td>TRP C6</td>
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Mitochondrial gene abnormalities cause podocyte damage.

- Primary coenzyme Q10 deficiency secondary to genetic defects in the COQ2 gene – “COQ2 nephropathy”. (1)
- Multiple others. (2)

FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases

Classification:
1. Primary (glomerular permeability factors).
2. Infectious (HIV, etc.).
3. Toxic (drug-induced).
4. Secondary (glomerular hyperfiltration, reduced renal mass, etc.).
5. Genetic (hereditary defects of podocyte proteins).

Predict
- recurrence in transplant
- response to TPE

Predict
- no recurrence in transplant
- no response to TPE
**FSGS (Focal Segmental Glomerulosclerosis)**

**Predicting post-transplant recurrence: genetic markers**

**Study patients:**
- 83 children with primary FSGS who received at least one renal allograft. (mean age 6.7 years at diagnosis; 13 years at first transplantation).
- 53 of these were analyzed for *NPHS2* mutations (gene for Podocin).

**Results:**
- FSGS recurred in 30 patients (36%) (median 13 days; range 1.5 to 152 days).
- 23 patients received a second kidney transplant, and FSGS recurred in 11 (48%) (median 16 days; range 2.7 to 66 days).
- Recurrence of FSGS: 0% (0 of 11) in patients with homozygous or compound heterozygous *NPHS2* mutations versus 45% in patients without mutations.

**Conclusion:**
- Genetic testing for pathogenic mutations may be important for prognosis and treatment of FSGS both before and after transplantation.

FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases

Classification:

1. Primary (glomerular permeability factors).
2. Infectious (HIV, etc.).
3. Toxic (drug-induced).
4. Secondary (glomerular hyperfiltration, reduced renal mass, etc.).
5. Genetic (hereditary defects of podocyte proteins).

Predict

- recurrence in transplant
- response to TPE

Predict

- no recurrence in transplant
- no response to TPE
At what anatomic sites could “glomerular permeability factors” act to cause reversible damage to the podocyte cytoskeleton?
Foot Process Effacement (FPE): role of Dynamin and Cathepsin L

Critical elements in maintaining podocyte foot-process integrity

- Dynamin
- Cathepsin L
- Actin
Foot Process Effacement (FPE): role of Dynamin and Cathepsin L

Evidence from a murine model

- Dynamin maintains FP structure by regulating Actin.
- Cathepsin L (Cat L) induces proteinuric kidney disease. Is increased in Hu proteinuric diseases. Is increased in a murine model.
- Cat L-deficient mice resist foot process effacement (FPE)

Gene delivery into normal mice:
- of a mutant Dynamin (that does not bind GTP) → induces FPE and proteinuria.
- of the Cat L-cleaved product of Dynamin → induces FPE and proteinuria.

Gene delivery into proteinuric mice:
- of 2 different Cat L-resistant Dynamin mutants → reverses proteinuria and FPE.

Foot Process Effacement (FPE): role of Dynamin and Cathepsin L

Evidence from a murine model

Foot Process Effacement (FPE) by “glomerular permeability factors”

Plasma from cases of recurrent FSGS has the same effect

- Proteinuria in experimental animals given FSGS plasma. (1)
- Shrinking of cultured glomeruli in vitro if FSGS plasma added. (2)
- This “Glomerular Volume Variation” (GVV) test has been standardized as a semi-quantitative research assay of permeability factor activity. (3)

Candidate molecules:

- Small, highly glycosylated, hydrophobic protein(s)/peptide(s) 30 to 50 kDa, poorly characterized. (1)
- Permeability activity is decreased by plasmapheresis. (2)
- Normal plasma contains substances that block or inactivate the FSGS permeability factor.
- In vitro, blocking by cyclosporine, indomethacin, etc.
- Proteinuric effect inhibited by galactose. (3)
- Clinical benefit in FSGS patients given oral galactose. (4, 5)

Glomerular permeability factors in recurrent FSGS

**Candidate molecule:**
**CLC1** (Cardiotrophin-like cytokine 1)

- CLC1 is a member of the interleukin-6 family (approx. 220 AA, 24kDa).
- Decreases nephrin expression in cultured podocytes.
- CLC1 inhibitors reverse the permeability effect of plasma from FSGS patients.
- Data are preliminary.

Recent research implicates “suPAR”, the soluble form of the urokinase receptor present on podocytes:

- suPAR levels (22 to 45 kDa fragments) are elevated in 70% of patients with FSGS, but not in other glomerular diseases.
- In animal models, suPAR causes podocyte injury by activation of β3 integrin.
- In kidney biopsies, β3 integrin is found on podocytes in patients with FSGS (but not other diseases).
suPAR removal by plasmapheresis in recurrent FSGS (post-transplant)

- Initial studies of plasmapheresis (TPE):
  - clinical remission if suPAR levels <2,000 pg/ml.
  - serum no longer induces podocyte β3 integrin.

- In 2 patients:
  - TPE failed to reduce suPAR levels <2,000 pg/ml.
  - did not achieve clinical remission.
  - serum still strongly activated β3 integrin.

Further evidence of pathogenic role of suPAR

Study patients: Two cohorts with biopsy-proven primary FSGS:
- 70 patients from the North America–based FSGS clinical trial (CT).
- 94 patients from European PodoNet study of steroid-resistant nephrotic syndrome.

Results:
- Elevated suPAR in 84.3% (CT) and 55.3% (PodoNet), versus 6% of controls (P=0.0001); inflammation did not account for this difference.
- Reduction of suPAR correlates with treatment and with reduction of proteinuria, with higher odds for complete remission (P=0.04).

Conclusions:
- suPAR levels elevated in geographically and ethnically diverse patients with FSGS.
- Reductions in suPAR levels correlate with different therapeutic regimens and with remission; this supports the role of suPAR in pathogenesis.

Unexpected finding:
- In the PodoNet cohort, patients with an NPHS2 mutation had higher suPAR levels than those without a mutation. (NPHS2 codes for Podocin.)

ACE-inhibitors, Angiotensin Receptor Blockers and ACTH(gel)

- Perhaps not just non-specific treatments for nephrotic diseases.
- ACTH (corticotrophin) is cleaved to α-MSH (melanocyte stimulating hormone) which binds to the receptor MC1R on the podocyte. (1)
- Angiotensin II regulates and enhances the expression of transient receptor potential cation channel 6 (TRPC6). (2)
- Antibodies to AT1 receptors on podocytes can cause proteinuria. (3)

TPE for post-transplant recurrence (slide 1 of 2):

- TPE is established first-line therapy (plus immunosuppression with mycophenolate, cyclophosphamide or rituximab).
- ASFA (2010) recommends initial regimen of TPE daily for 3 days, then at least 3 times per week for the next 2 weeks (1). Thereafter, TPE can be continued 2 - 3/week until remission occurs, as judged by serial quantitation of urine protein and serum creatinine. (2)
- One series performed 17 TPE treatments in each of 7 adults, all of whom had functioning grafts 10 months later. (3)
- Other series claim remission rates up to 80% in adults (4), and 88% in children. (5)

TPE for post-transplant recurrence (slide 2 of 2):

- One large retrospective series concluded that:
  - Modern post-transplant immunosuppressive drug regimens do not reduce the recurrence rate of FSGS in adults.
  - However, TPE achieved remission in 75% of cases. (1)

- Patients receiving treatment for recurrent FSGS or preemptively (for high-risk profile):
  - Of the different treatment approaches, TPE combined with rituximab (anti-CD20) was most associated with prolonged remission of proteinuria. (2)


Indications for plasmapheresis for FSGS

TPE for peri-transplant prophylaxis:

- 10 patients at high risk because of rapid progression (4) or prior recurrence in a transplant (6) received 8 TPE treatments in the peri-operative period.
  - 3 had recurrence within 3 months (all had prior graft loss to recurrence); 2 developed ESRD, 3rd with significant renal dysfunction.
  - 7 (including 3 with prior graft loss to recurrence) were free of recurrence at follow-up (238–1258 days), mean creatinine 1.53 mg/dL. (1)

- More recently, in 34 pediatric transplant cases, prophylactic TPE post-transplant appeared not to confer any outcome benefit compared with treatment of actual recurrence. (2)

Indications for plasmapheresis for FSGS

TPE for primary FSGS (in native kidneys):

- TPE (averaging 17 treatments) plus corticosteroids and cyclophosphamide achieved sustained remissions in 8 of 11 previously unresponsive adults. (1)
- TPE (six treatments) without consistent immunosuppressive drugs reduced proteinuria in only 2 of 8 patients. (2)
- Expert opinion “based on very limited experience” (3):
  “Consider TPE for
  • Severe disease manifestations despite an adequate trial of initial immuno-suppressive therapy, in which very high levels of circulating permeability factor have been demonstrated.
  • Continued massive proteinuria and hypoalbuminemia despite exposure to an adequate course of prednisone, cyclosporine, and mycophenolate.”

(3) Appel GB and Cattran DC. Treatment of primary FSGS. In “UpToDate” ® online.
Type of plasmapheresis for FSGS

Conventional plasma exchange (plasma removal and replacement):

- Established first-line treatment for recurrent FSGS (1-9)
- Removes macromolecules of all sizes:
  - IgG (140 kDa)
  - suPAR (22 to 45 kDa)
  - Ill-defined permeability factors (30 to 50 kDa)
  - CLC1 (24 kDa), etc., etc.

(1) Zimmerman SW: Nephron 40:241-245, 1985
Type of plasmapheresis for FSGS

Immunoadsorption (IA) plasmapheresis:

**Protein A columns**
- Reported as effective for recurrent FSGS (1)
- Removes IgG, but probably not small proteins like suPAR, etc.

**Anti-IgG columns**
- Reported as effective for recurrent FSGS (2, 3)
- Removes IgG, but probably not small proteins like suPAR, etc.

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Double-filtration (cascade) plasmapheresis:
- Returns albumin (67 kDa) and all smaller molecules to the patient.

**#1: Plasma-filter**
- Pore size: large
- Cut-off: >1000 kD

Membrane specifications are those of Asahi products
(Asahi Kasei Kuraray Medical Co., Tokyo 101-8,101, Japan)

Diagram from Ward DM,
J Clin Apheresis
26:230-238, 2011

**#2: Plasma-fractionator**
- Pore size: medium
- Cut-off: ~ 100 kD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular Mass</th>
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<tr>
<td>IgM</td>
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<tr>
<td>IgG</td>
<td>~ 140 kDa</td>
</tr>
<tr>
<td>Albumin</td>
<td>~ 67 kDa</td>
</tr>
<tr>
<td>suPAR</td>
<td>~22-45 kDa</td>
</tr>
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Type of plasmapheresis for FSGS

Tryptophan adsorption column:
- “Effective for steroid resistant FSGS”. (1)

LDL-apheresis:
- Reduces proteinuria in some cases. (2,3)

Update on immunoglobulin-binding IA columns:

- IgG-binding columns are specifically designed to extract only immunoglobulins. Example – Globaffin ® columns use peptide ligand PGAM146 (Fresenius, Germany). (1)

- However, there is evidence from one case report that Immunoadsorption (IA) using Globaffin reduced suPAR also. The authors speculate that suPAR may bind to immunoglobulin molecules. (2)

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Plasma exchange vs. Immunoadsorption (anti-IgG column)

(TPE) = conventional plasmapheresis replacing with FFP and 5% albumin (1 to 1.5 x PV).

(IA) = immunoadsorption plasmapheresis with Globaffin® columns (2 to 2.5 x PV)

Plasma exchange vs. Immunadsorption (anti-IgG column)

*“Podocyte AP5 activity” = bioassay for podocyte β3 integrin activation by AP5 staining quantitated by mean fluorescence intensity (MFI)

Type of plasmapheresis for FSGS

Questions:

- Are recurrent types of FSGS due to suPAR or other small molecules that are not removed by immunoadsorption (IAPP) or double-filtration (DFPP)?
- Does the effectiveness of rituximab, corticosteroids and other immunosuppressants suggest a humoral immune mechanism?
Angiotensin Antibodies (AT1R) and FSGS

Alachkar N et al. NEJM 2013 368:971-973
Type of plasmapheresis for FSGS

Questions:

- Are recurrent types of FSGS due to suPAR or other small molecules that are not removed by immunoadsorption (IAPP) or double-filtration (DFPP)?
- Does the effectiveness of rituximab, corticosteroids and other immunosuppressants suggest a humoral immune mechanism?

Possible answers:

- There is secure evidence that whole plasma removal (TPE) is of major clinical benefit in FSGS (post-transplant recurrent type).
- If DFPP or IAPP are effective, it may imply mechanisms other than (or as well as) removal of suPAR, etc., in some cases.
- Plasmapheresis modalities other than conventional TPE have an uncertain mechanism of action in FSGS, and need further research.
- Until there is clarification, conventional plasma exchange (TPE) is the recommended apheresis modality (1)

FSGS, suPAR and selective plasmapheresis

SUMMARY:

1. **Recurrence of FSGS** after kidney transplant, and evidence for endogenous circulating permeability factors.
2. FSGS is common.
3. FSGS and West African genes that promote glomerular damage.
4. FSGS is a group of diseases.
5. **Podocyte foot-process architecture** and diseases due to genetic abnormalities of podocyte proteins.
6. **Podocyte foot-process damage** due to circulating permeability factors.
7. **Candidate molecules**: 30-50 kDa factors, CLC1, suPAR.
8. **Indications for TPE for FSGS**: Post-transplant recurrence, peri-transplant prophylaxis, native-kidney FSGS.
9. **Type of plasmapheresis for FSGS**: SuPAR, etc., are small macro-molecules (<50 kDa). What are the implications of reported successes using immunoadsorption, cascade filtration, etc.?
10. Non-selective TPE is recommended.
Thank you for your attention
Study patients:
- 1573 kidney transplant recipients.
- 5.0% carried some diagnosis of FSGS
- But only 1.9% (n=30) met strict diagnostic criteria for primary FSGS including biopsy-proven FSGS, lack of secondary factors, negative family history, and progression to ESRD within 10 years.

Results:
- In the strict criteria group, FSGS recurred in 47%.
- In patients not meeting strict criteria, FSGS recurred in 8% (P 0.001).
- Recurrence more common in children (86%) than adults (35%) (P 0.01).
- Graft survival was lower for primary FSGS than all others; the whole difference was due to recurrence.