Εστιακή Τμηματική Σπειραματοσκλήρυνση (FSGS)

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athens-NEPHROLOGY

Classifications of FSGS: Primary vs. Secondary

- Permeability Factor (100% foot process effacement)
- Idiopathic
- Autoimmune (T-cell response)

- Toxins
- Genetic Abnormalities
- Infections (HIV, Parvo B-19)
- Obesicity
- Heroin Nephropathy
- Familial Disease
- Drug Toxicity (pamidronate)

FSGS (Focal Segmental Glomerulosclerosis)

Clinical features:

- Mainly children, teenagers and young adults.
- Proteinuria, sometimes persistent hematuria.
- Nephrotic syndrome* in almost 100% of "Primary" type FSGS, ~ 50% of other subtypes of FSGS.
- Often hypertensive.
- Progressive renal failure: 70% reach end stage in 10 years.
- Recurs in kidney transplants (only "Primary" type FSGS)

*Nephrotic syndrome =
heavy proteinuria (e.g. >3.5 g/day), enough to cause low serum albumin (e.g. <3 g/dL), low enough to cause edema, and also to cause secondary hypercholesterolemia.

FSGS (Focal Segmental Glomerulosclerosis)

Treatment:

- 20 - 40% of nephrotic cases may be helped by corticosteroids.
- Data also support use of
  - cyclosporine,
  - mycophenolate,
  - cyclophosphamide,
  - rituximab, etc.
- Use ACE-inhibitors or ARB's (non-specific).
- Role of therapeutic apheresis

	TPE	LDL-apheresis*
• for post-transplant FSGS	Established (ASFA Category 1)	Meagre evidence
• for native-kidney 1^{y} FSGS	Less evidence	Some evidence

* LDL-apheresis using dextran sulfate adsorption (Kaneka Liposorber®)

FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases of the renal glomeruli:

- Actually a pattern of response to injury that has multiple etiologies.
- The "Primary" type recurs in kidney transplants.

1972

RECURRENCE OF IDIOPATHIC NEPHROTIC SYNDROME AFTER RENAL TRANSPLANTATION

JOHN R. HOYER, LEOPOLDO RAIJ, ROBERT L. VERNIER, RICHARD L. SIMMONS, JOHN S. NAJARIAN, ALFRED F. MICHAEL

Departments of Pediatrics, Internal Medicine, and Surgery, University of Minnesota Medical School, Minneapolis, Minnesota 55455, U.S.A.

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 œdema 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-

Hoyer JR, et al. *Lancet.* ii: 343-348, 1972

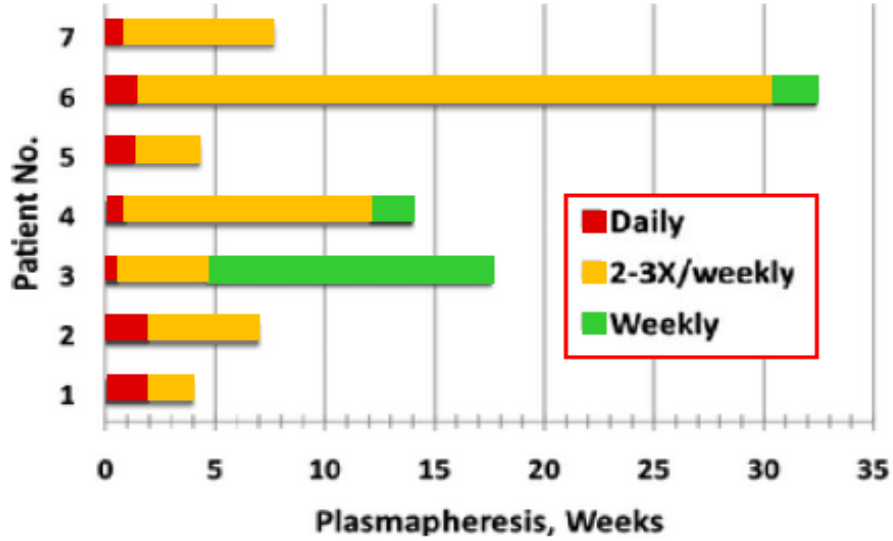
FSGS

2016

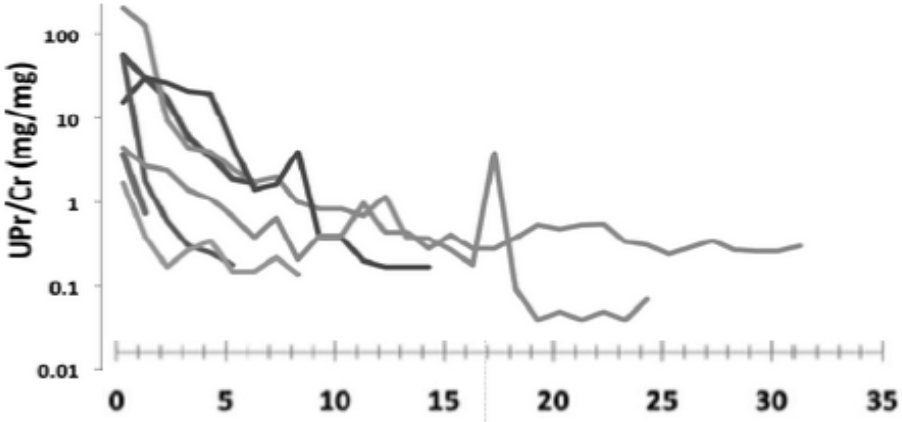
- TPE is established first-line effective treatment for recurrence of FSGS after renal transplantation

Straatmann C, et al. Success with plasmapheresis treatment for recurrent FSGS in pediatric renal transplant recipients. *Pediatric Transplantation 18:29-34, 2014*

Frequency of TPE



Response (Proteinuria)



Plasma exchange (TPE) for FSGS

for recurrent FSGS:

- Recurs post-transplant in ~ 23% of adults with primary FSGS.
- Recurrence rates higher in children.
- Recurrence rates higher if previous transplant loss to recurrence.
- TPE for post-transplant recurrence is well established (1-11).

for native-kidney FSGS:

- . . . less evidence.

(1) Zimmerman SW: *Nephron* 40:241-245, 1985
(2) Valdivia P, et al. *Transplant Proc* 37:1473-1474, 2005
(3) Schachter ME, et al: *Clin Nephrol* 74:173-181, 2010
(4) Ponticelli C, Glassock RJ: *Clin J Am Soc Nephrol* 5:2363-2372, 2010
(5) Moroni G, et al. *Transpl Int* 23:208-216, 2010
(6) Gungor O, et al. *Transplant Proc* 43:853-857, 2011
(7) Tsagalis G, et al. *Artif Organs* 35:420-425, 2011
(8) Gonzalez E, et al. *Pediatr Transplant* 15:495-501, 2011
(9) Straatmann C, et al. Pediatric Transplantation 18:29-24, 2014
(10) Paglialonga F, et al. Pediatr Nephrol 30:103-111, 2015

18ο Πανελλήνιο Συνέδριο Νεφρολογίας

Ρ 59 ΚΛΙΝΙΚΗ ΕΚΒΑΣΗ ΚΑΙ ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΕΣΤΙΑΚΗ ΤΜΗΜΑΤΙΚΗ ΣΠΕΙΡΑΜΑΤΟΣΚΛΗΡΥΝΣΗ ΜΕΤΑ ΑΠΟ ΜΕΤΑΜΟΣΧΕΥΣΗ ΝΕΦΡΟΥ

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[2]University Hospital "Queen Elizabeth", Birmingham, UK

Σκοπός: Η υποτροπή νεφρωσικού συνδρόμου μετά από νεφρική μεταμόσχευση σε ασθενείς με εστιακή τμηματική σπειραματοσκλήρυνση (ΕΤΣΣ) παραμένει μία συχνή και απρόβλεπτης εξέλιξης επιπλοκή. Οι παράγοντες κινδύνου υποτροπής δεν έχουν ξεκάθαρα αναγνωρισθεί. Η παρούσα μελέτη σχεδιάσθηκε για να αναλύσει την κλινική έκβαση και τους παράγοντες κινδύνου υποτροπής για ΕΤΣΣ σε ασθενείς μετά από μεταμόσχευση νεφρού.

Υλικό-Μέθοδοι: Αναδρομικά μελετήθηκαν δεδομένα από 31 ασθενείς με ΕΤΣΣ, οι οποίοι υποβλήθηκαν σε μεταμόσχευση νεφρού σε διάστημα 5 ετών.

Αποτελέσματα: Υποτροπή νεφρωσικού συνδρόμου παρατηρήθηκε σε 7 λήπτες νεφρικού μοσχεύματος (22,6%). Οι δότες των ασθενών που υποτροπίασαν ήταν νεώτεροι (32 ετών) από τους υπόλοιπους δότες (64 ετών). Παράλληλα και οι λήπτες που υποτροπίασαν ήταν νεώτεροι (μέση ηλικία 36 έναντι 44 ετών). Ο χρόνος ψυχρής ισχαιμίας στους ασθενείς που υποτροπίασαν ήταν 9 ώρες ενώ στους υπολοίπους 15 ώρες. Η ΕΤΣΣ εμφανίσθηκε μετά την μεταμόσχευση κυρίως στους ασθενείς με ιστορικό ιδιοπαθούς ΕΤΣΣ. Οξεία απόρριψη εμφανίσθηκε μόνο σε έναν ασθενή με υποτροπή (14%), ενώ στην υπόλοιπη ομάδα των ασθενών παρατηρήθηκε σε 6 (25%). Και οι 7 λήπτες μοσχεύματος στους οποίους επανεμφανίσθηκε η ΕΤΣΣ υποβλήθηκαν ο καθένας σε 10 κατά μέσο συνεδρίες πλασμαφαίρεσης. 4/24 (16,6%) και 4/7 (57%) από τις δύο ομάδες ασθενών υπέστησαν απώλεια νεφρικού μοσχεύματος.

Συμπέρασματα: Ασθενείς με ιδιοπαθή ΕΤΣΣ που υποβλήθηκαν σε μεταμόσχευση νεφρού έχουν εξαιρετικά αυξημένες πιθανότητες υποτροπής της νόσου. Σε αυτές τις περιπτώσεις η επιβίωση του νεφρικού μοσχεύματος είναι μικρότερη. Σε αντίθεση με άλλες μελέτες η ηλικία του δότη δεν παρουσιάζεται ως παράγων κινδύνου για υποτροπή της νόσου. Τα ευρήματα μας συνηγορούν με μεμονωμένα ευρήματα της βιβλιογραφίας όπου επεισόδια οξείας απόρριψης δεν εμφανίζονται συχνά σε ασθενείς με υποτροπή της νόσου.

FSGS (Focal Segmental Glomerulosclerosis)

Primary FSGS:

- Plasma from patients with Primary FSGS can cause:
  - Proteinuria in experimental animals.
  - Shrinking of cultured glomeruli in vitro.
- Due to endogenous circulating glomerular permeability factor(s).
- Candidate molecules, none proven:
  - Small, highly glycosylated, hydrophobic protein(s) / peptide(s), 30 to 50 kDa, poorly characterized.
  - suPAR (soluble urokinase-type Plasminogen Activator Receptor).
  - CLC1 (Cardiotrophin-like cytokine 1).
  - others

  Note all are < 50 kDa (molecular weight)

McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol 5:2115-2121, 2010*

Am J Physiol Renal Physiol 296: F947–F956, 2009.
First published January 7, 2009; doi:10.1152/ajprenal.90601.2008.

Glomerular endothelial cell fenestrations: an integral component of the glomerular filtration barrier

Simon C. Satchell[1] and Filip Braet[2]

[1]*Academic Renal Unit, University of Bristol, Southmead Hospital, Bristol, United Kingdom; and* [2]*Australian Key Centre for Microscopy and Microanalysis, The University of Sydney, New South Wales, Australia*

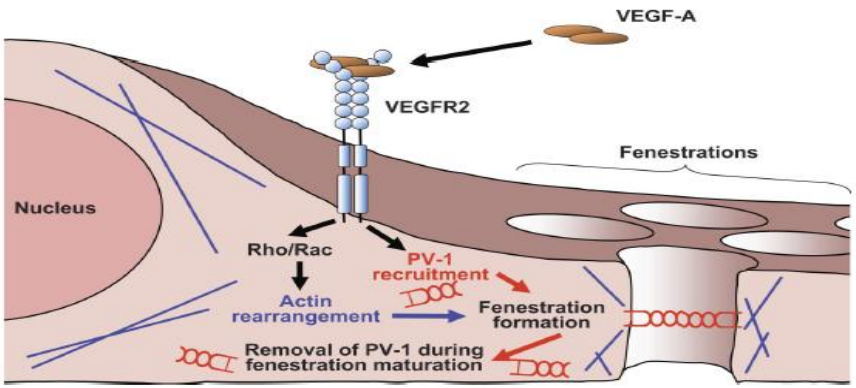
Table 1. ***Comparison of the three types of endothelial cell fenestrations***

	Endothelium in Which Fenestrations are Expressed		
	Systemic capillaries, e.g.,gastrointestinal and renal peritubular	"Discontinuous" endothelium, e.g.,hepatic sinusoidal	Glomerular
Endothelial type	Fenestrated	Discontinuous	Fenestrated
Diaphragm	Yes	No	No
Diameter, nm	60–70	100–175	60–80
PV-1 expression	Yes	No (only in development)	No (only in development)
Cytoskeletal ring	?	Yes	?
Cholesterol ring	?	Yes	?
Basal lamina	Yes	No	Yes
Glycocalyx	Yes	?	Yes

PV-1, plasmalemmal vesicle-associated protein-1; ?, unknown.

What Factors Stimulate the Development of Fenestrations?

The observation that high levels of VEGF expression are found in epithelial cells closely associated with fenestrated endothelia led to the hypothesis that VEGF induces endothelial fenestrations (25, 44). This hypothesis has been investigated



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Review

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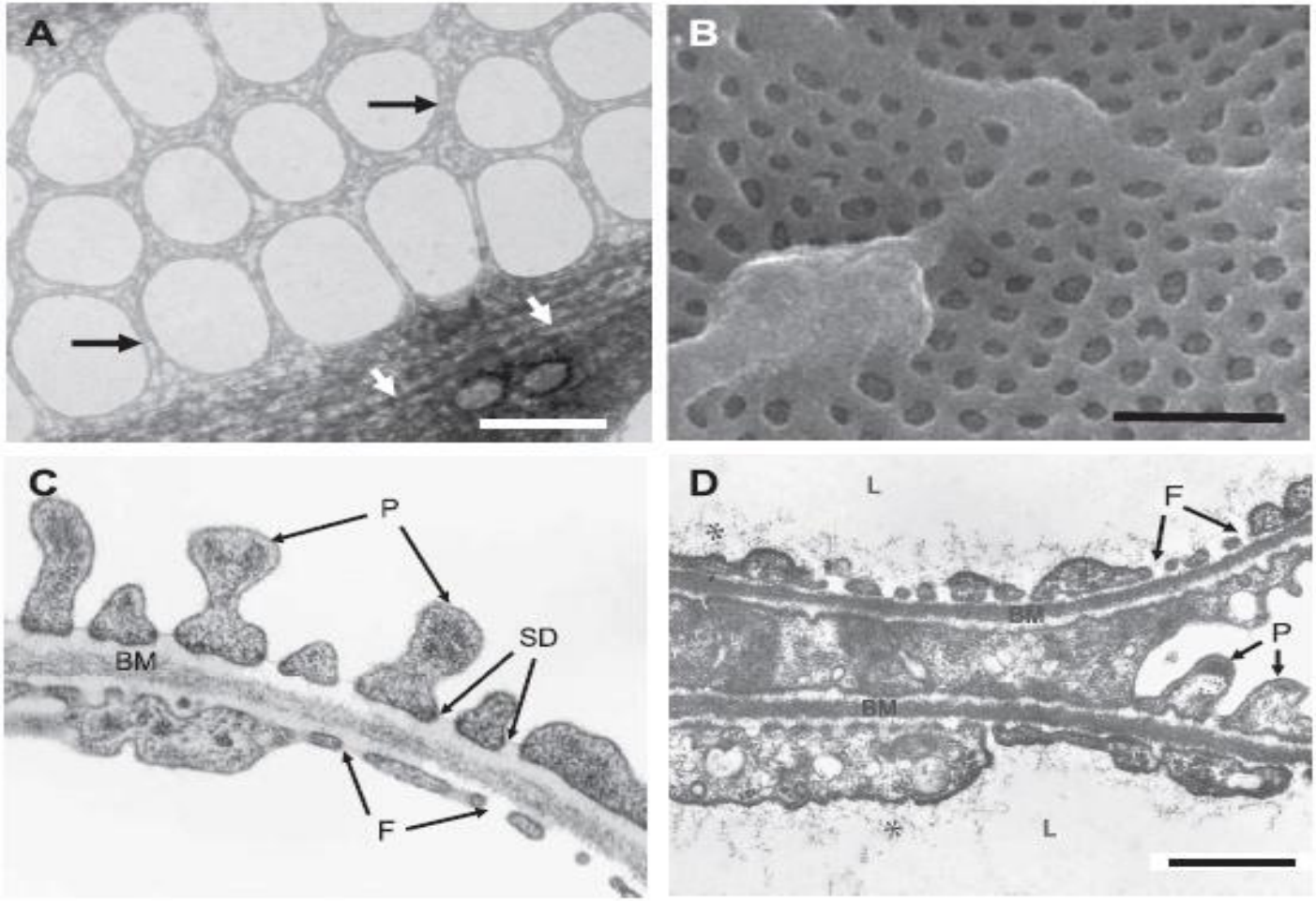

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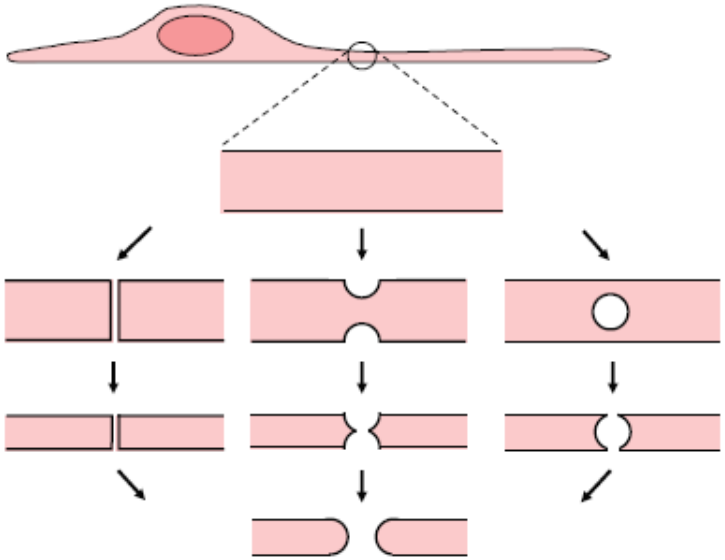
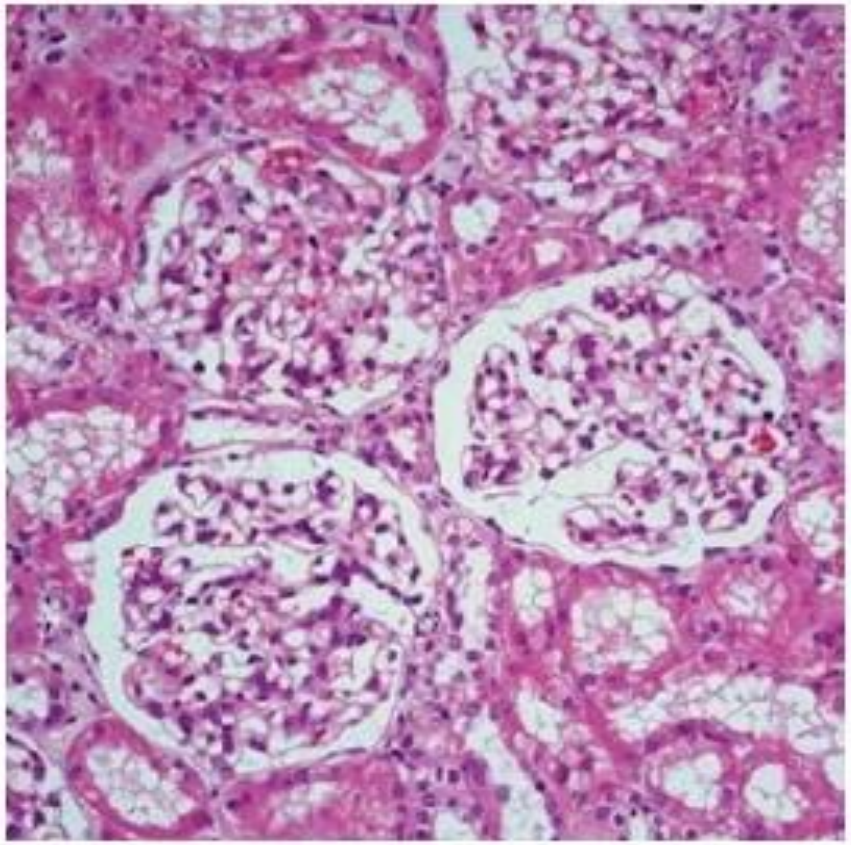
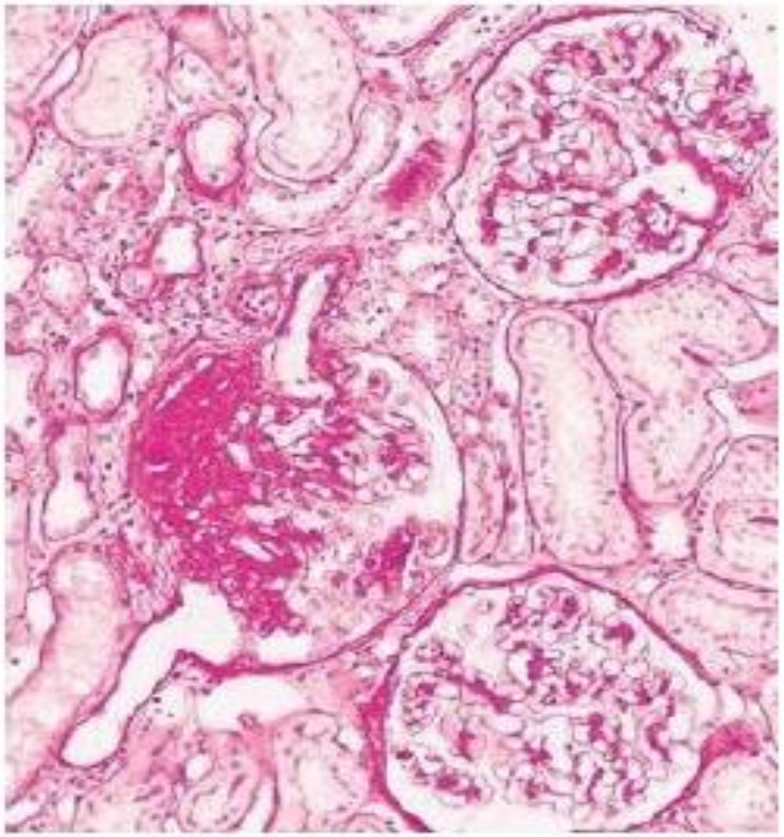


Normal Glomeruli



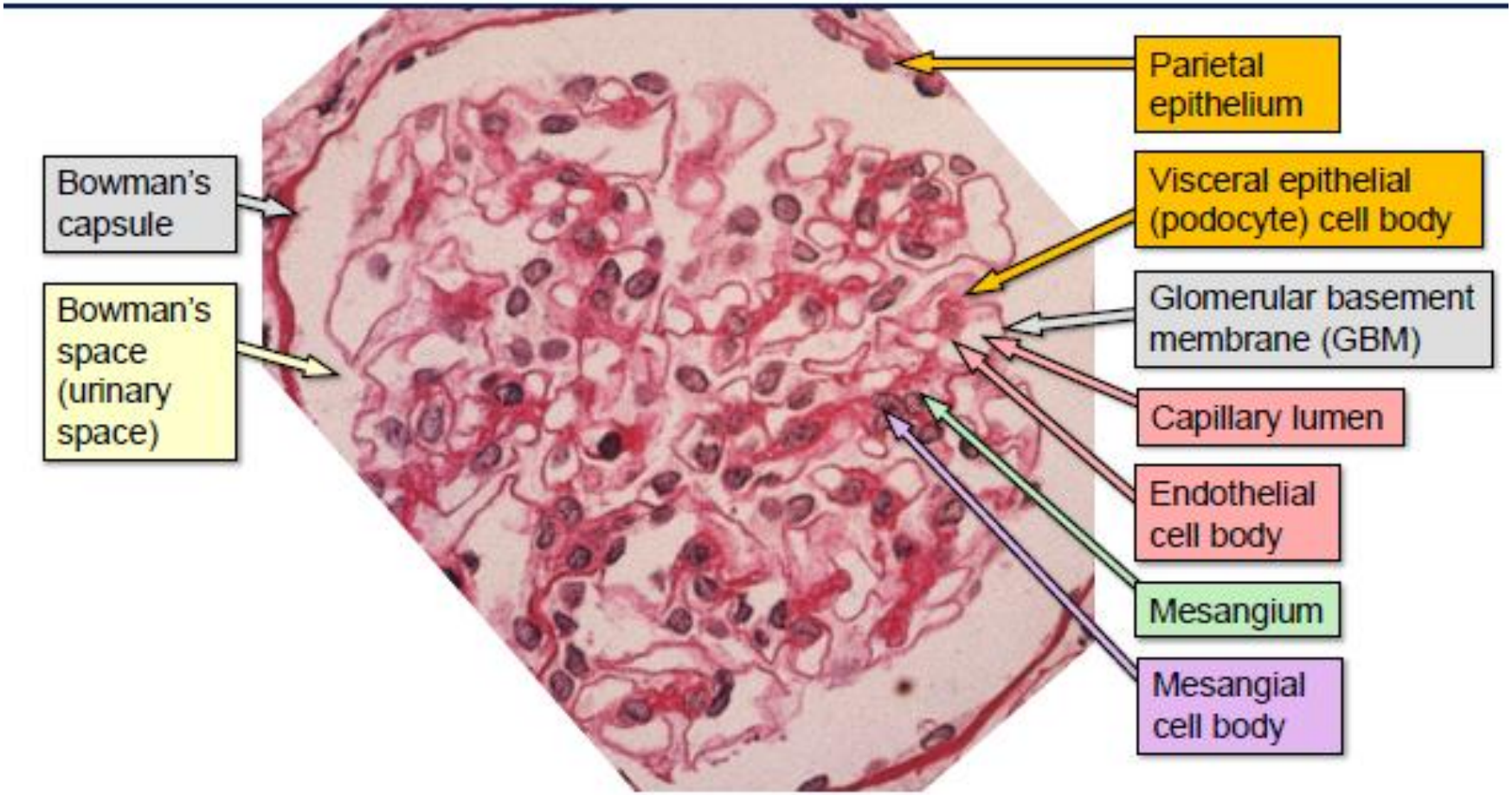
FSGS



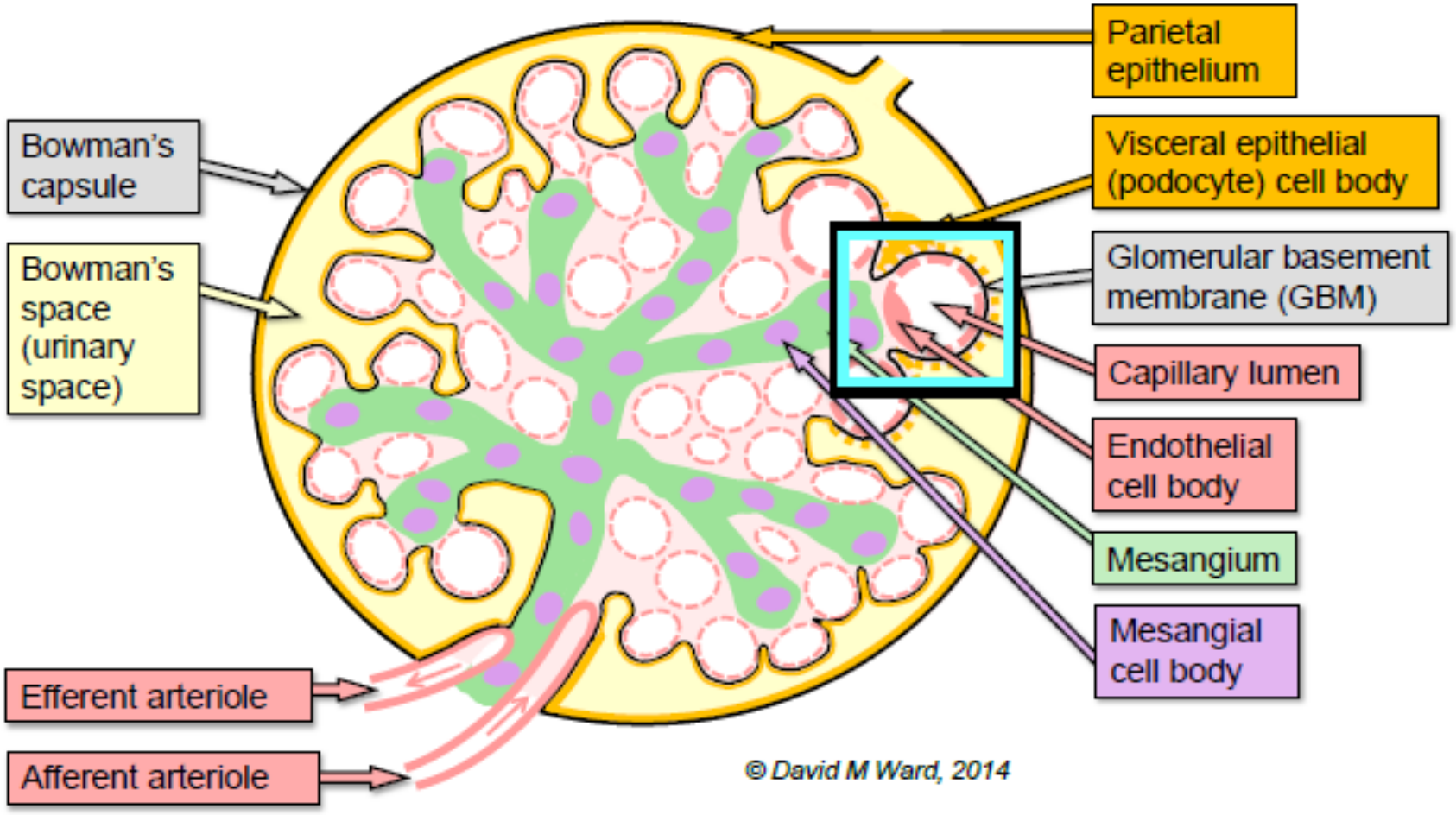
Focal = some glomeruli not affected

Segmental = some parts not affected

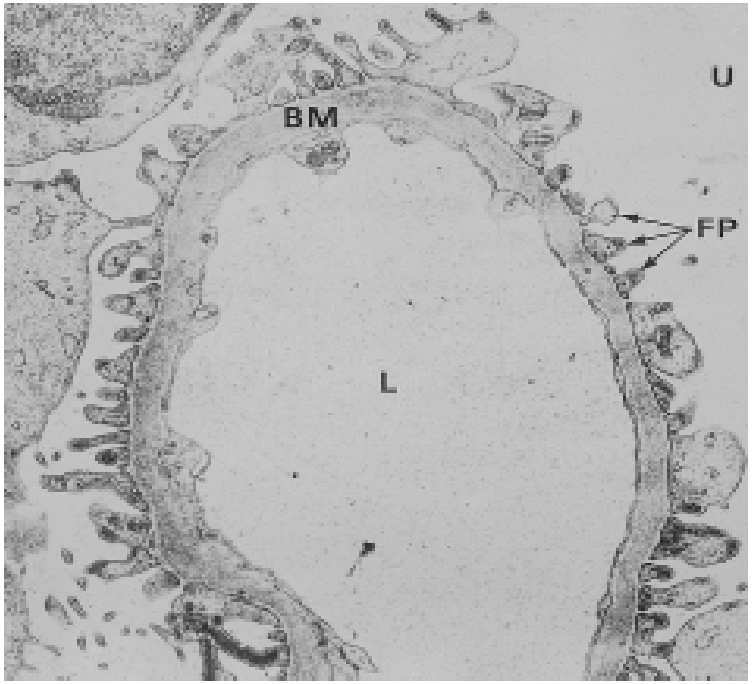
Normal Glomerulus

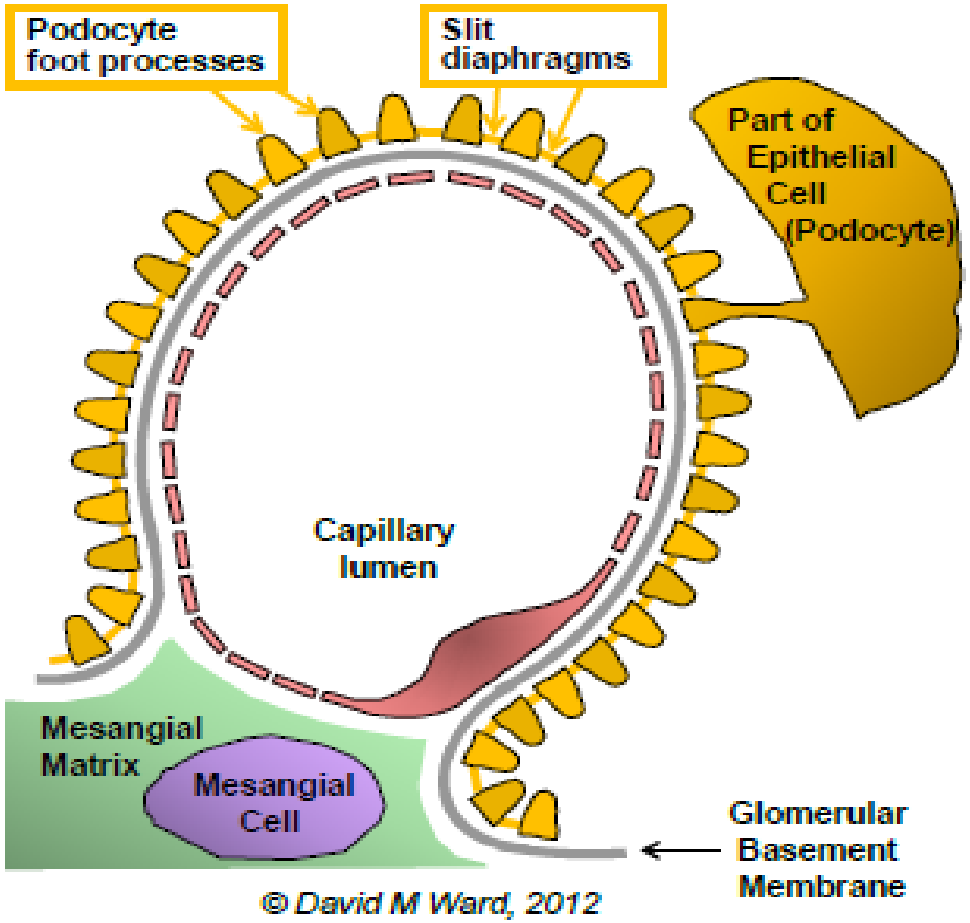


Normal Glomerulus - Diagram



Normal Glomerular Capillary Loop





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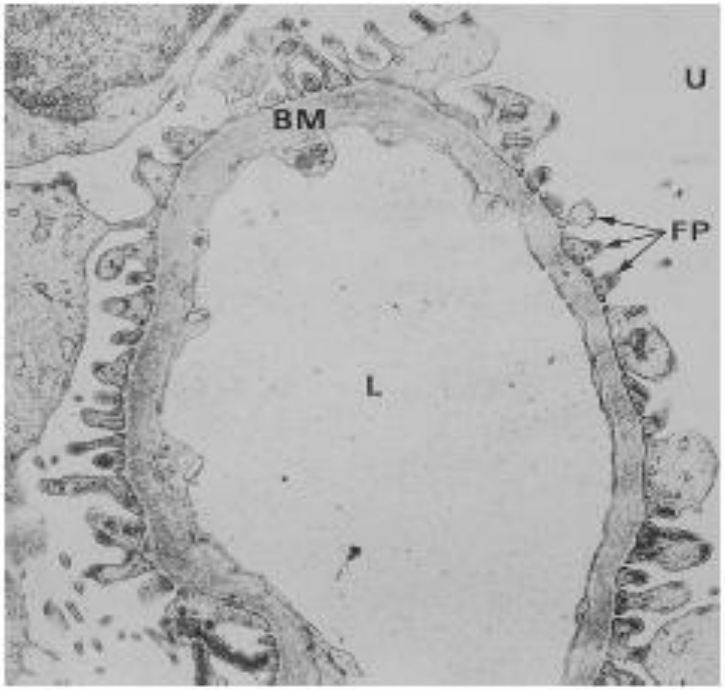
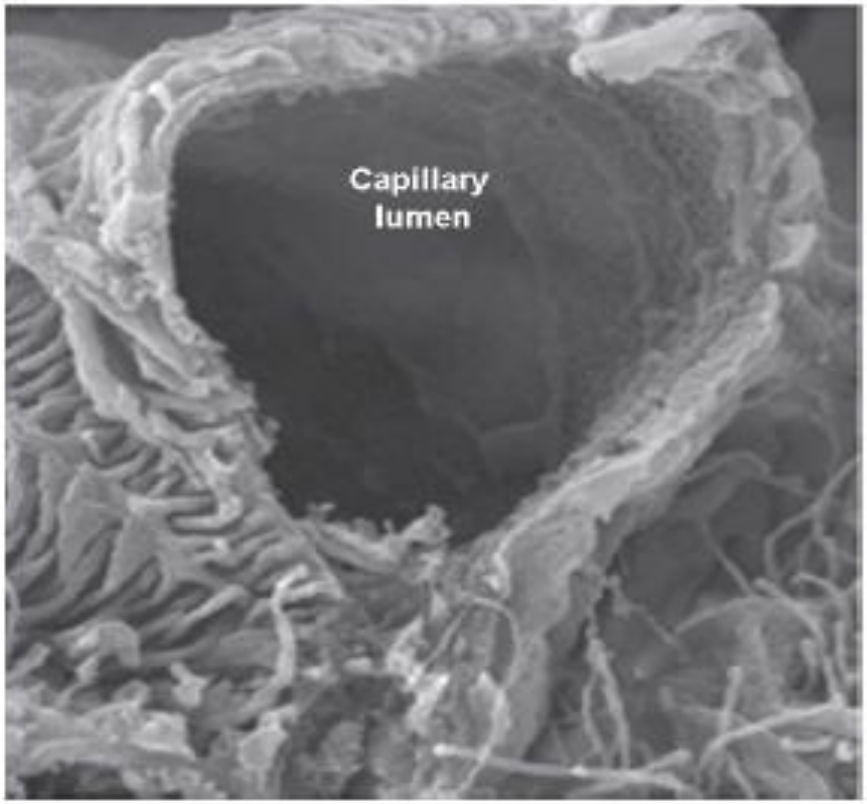
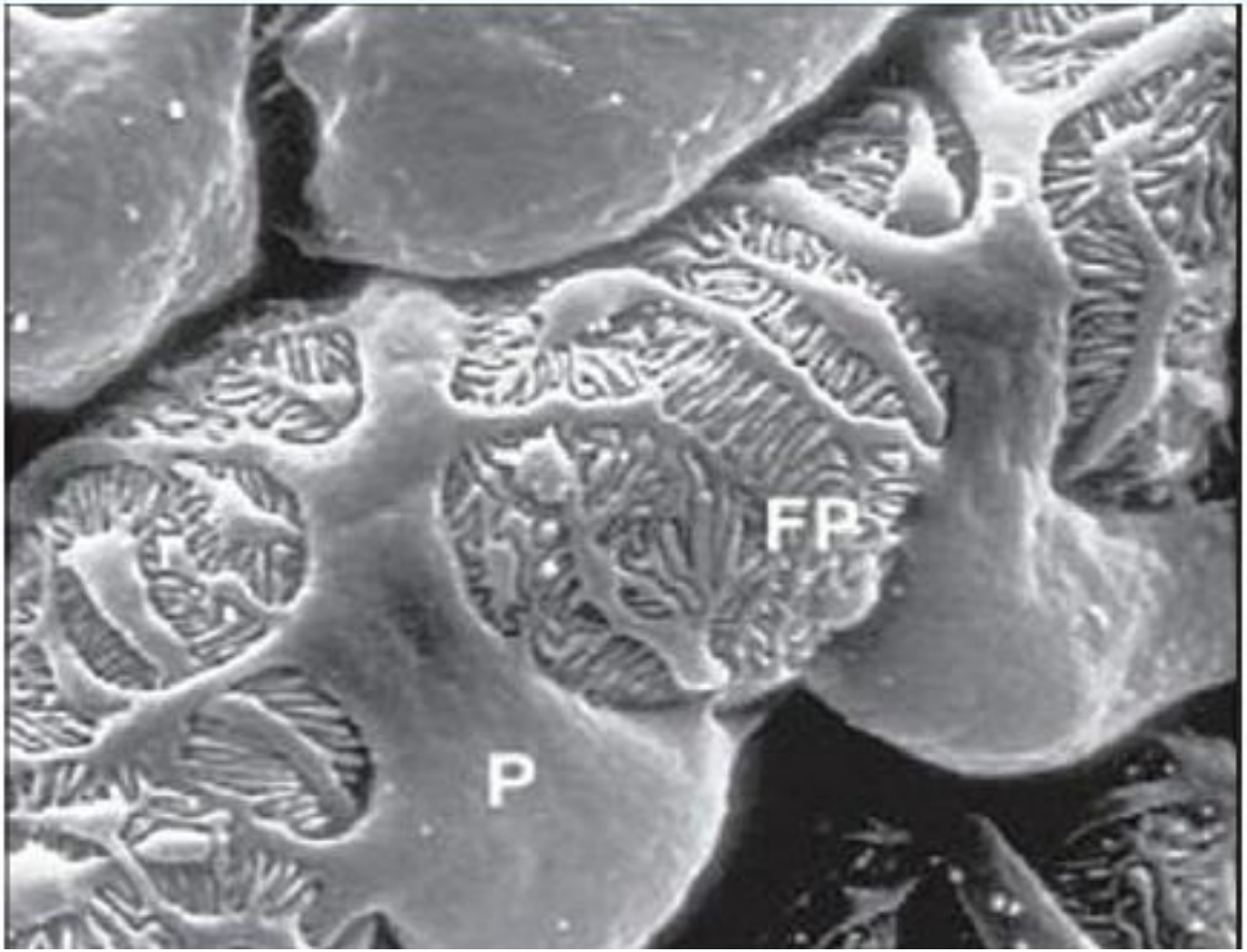
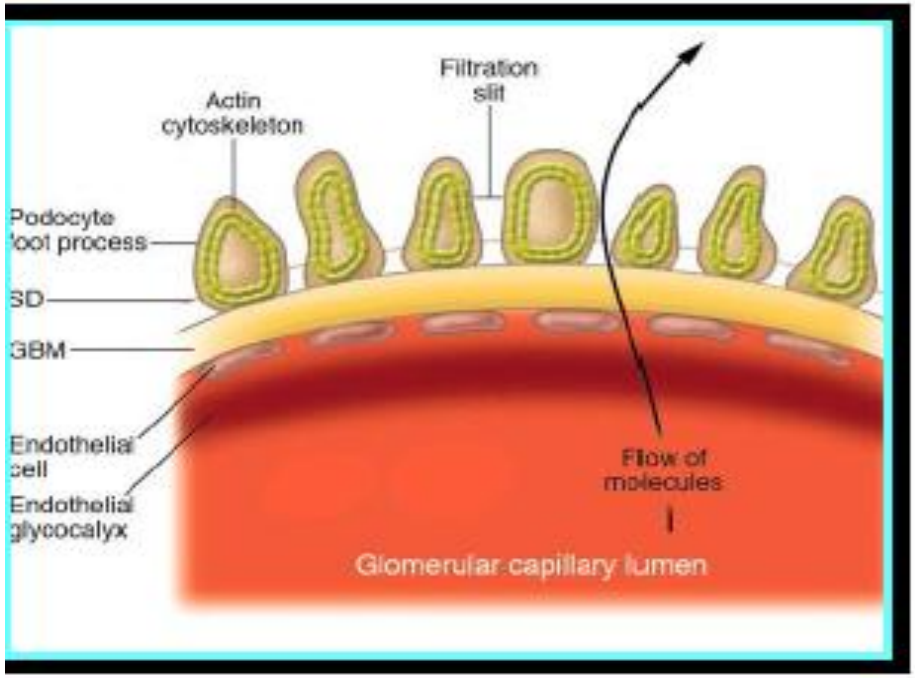




Podocyte Foot Process Architecture



Normal Glomerular Capillary Loop



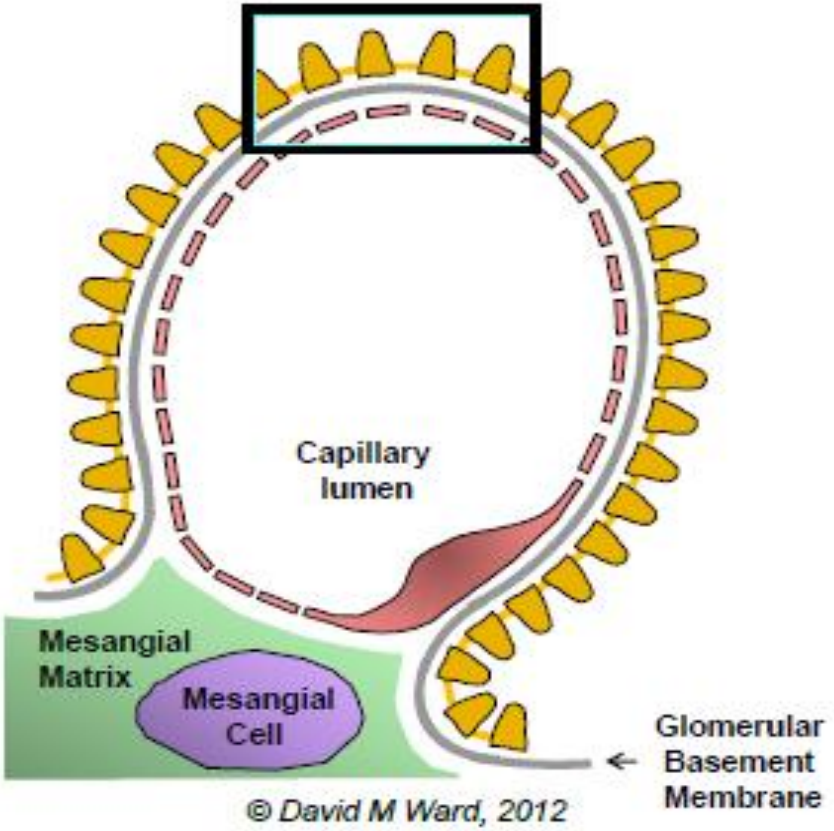
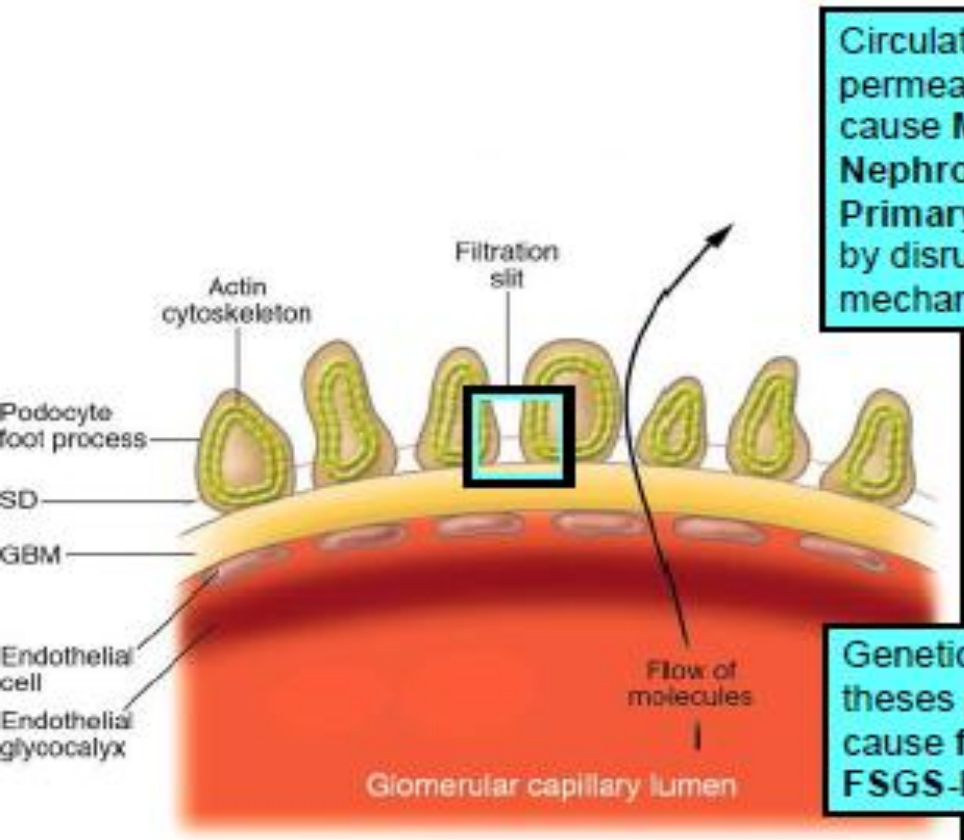
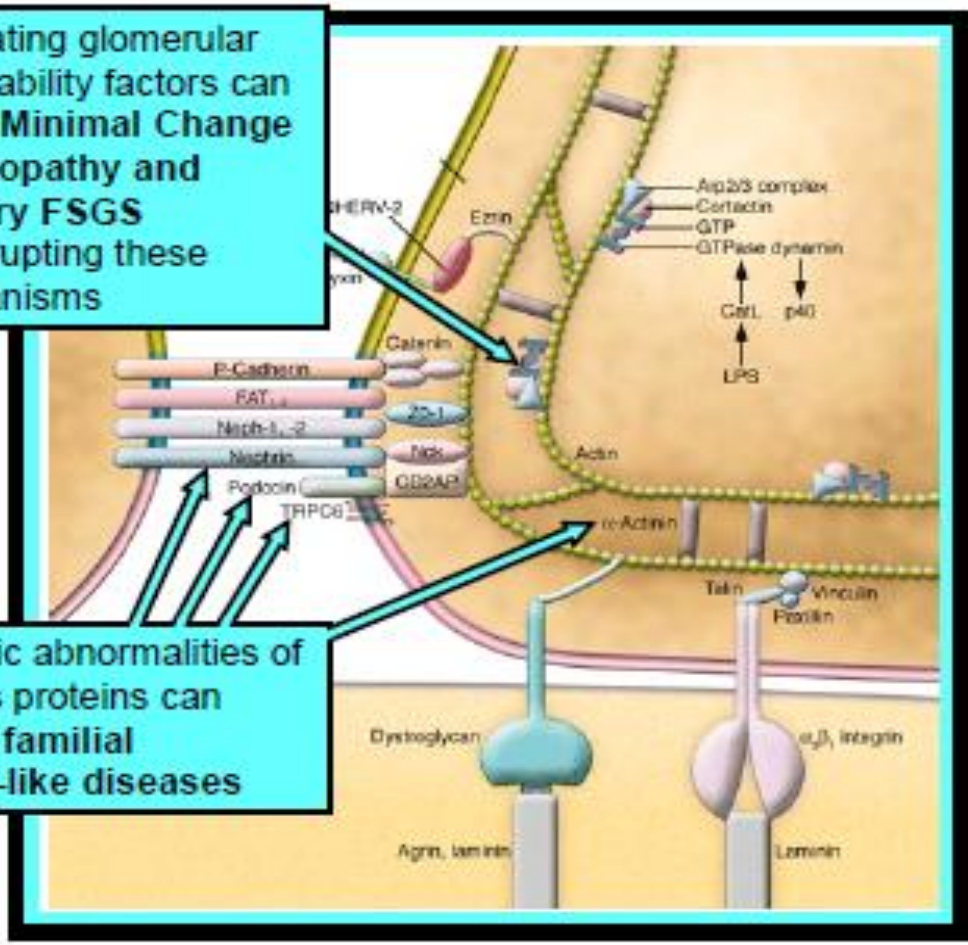


Illustration from Sever S et al, J Clin Invest 117:2095, 2007

Podocyte Foot Process Architecture



Circulating glomerular permeability factors can cause **Minimal Change Nephropathy and Primary FSGS** by disrupting these mechanisms

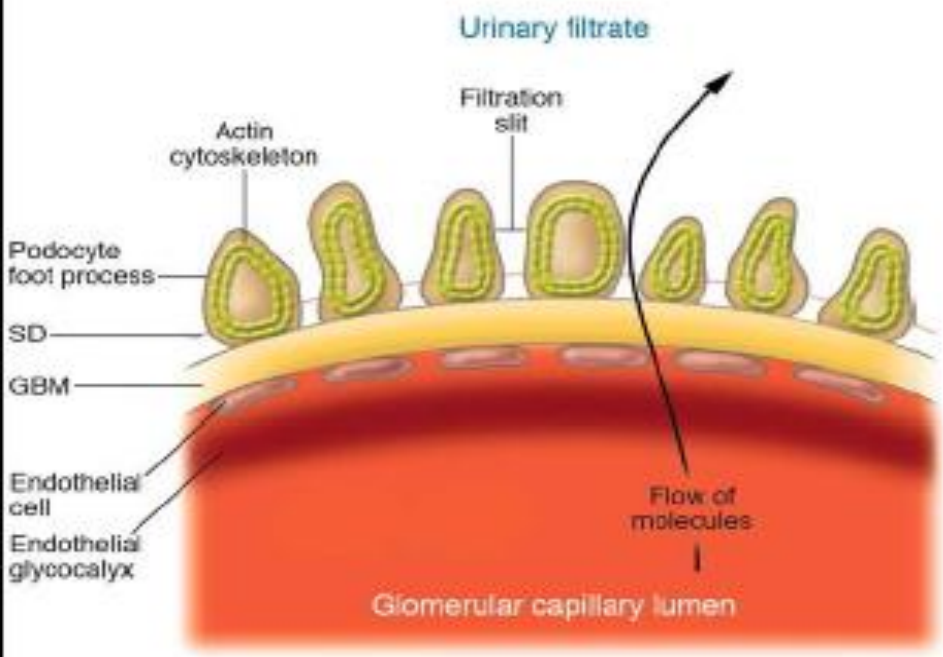


Genetic abnormalities of theses proteins can cause **familial FSGS-like diseases**

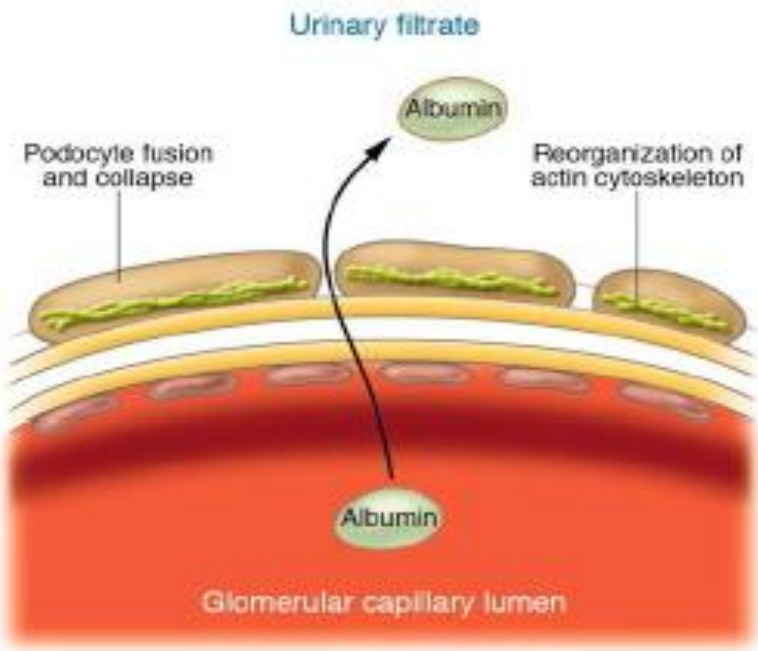
Illustrations from Sever S et al, J Clin Invest 117:2095, 2007 and Ronco P, (editorial) J Clin Invest 117:2081, 2007

Podocyte Foot Process Effacement

Healthy:



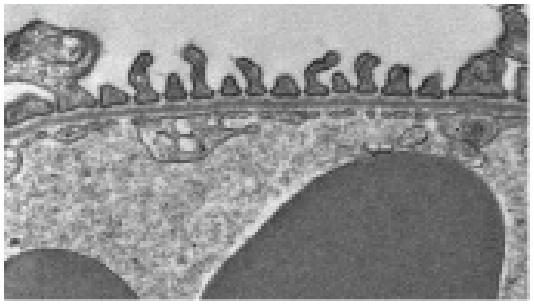
Collapsed / "effaced":

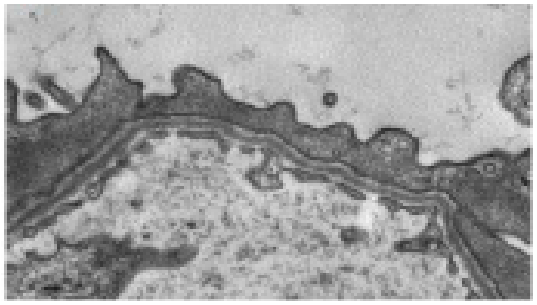


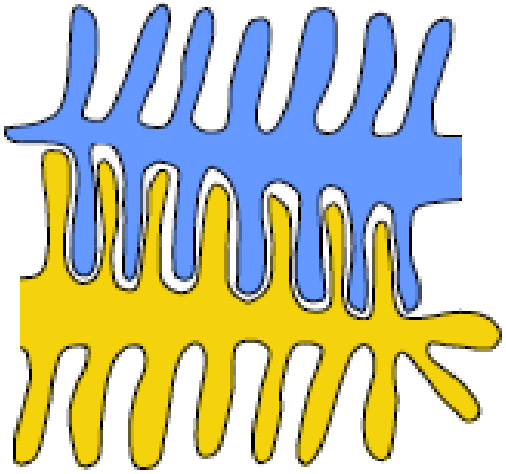
Illustrations from Sever S et al, J Clin Invest 117:2095, 2007 and Ronco P, (editorial) J Clin Invest 117:2081, 2007

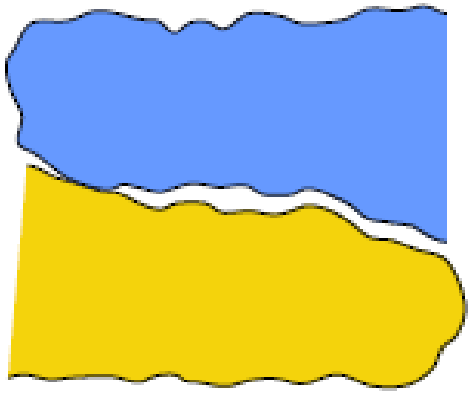
- Injury to visual epithelial cell or podocyte, which attaches to the glomerular basement membrane by discrete foot process, appears to be the primary problem in most forms of FSGS
- Barrier to filtration is lost

Podocyte Foot Process Effacement









In Minimal Change Disease:

- podocyte effacement is reversible with steroids

In Primary FSGS:

- podocyte effacement
- progresses to podocyte cell death
- with consequent sclerosis of the underlying glomerular capillary tuft.

Electron micrographs courtesy Dr Lindskog Johnsson 2014

FSGS is a group of diseases

	Etiology/ mechanism
Primary FSGS	Circulating factors toxic to podocyte integrity.
Secondary FSGS	Adaptive injury (hyperfiltration damage).
Familial FSGS	Genetic defects of podocyte and slit-pore proteins.
"Collapsing" form of FSGS	Toxins & viruses (HIV, parvo B19, pamidronate, etc.)
FSGS due to scarring from other GN	Non-specific scarring after inflammatory types of glomerulonephritis.

FSGS is more common in African Americans.

"**Good gene, bad gene.** The same gene variants that promote destruction of the kidney's filtration units also combat *Trypanosoma brucei rhodesiense* parasites".

- Two *APOL1* variants are common in West African chromosomes.
- These variant genes produce a serum factor that lyses trypanosomes.
- But confers FSGS odds ratio of 10.5
- And hypertension-attributed ESRD odds ratio of 7.3

Genovese G, et al. Science 329:841-845, 2010
Leslie M. Science 329:263, 2010 (Editorial)

FSGS is a group of diseases

	Etiology/ mechanism	Histological hallmarks
Primary FSGS	Circulating factors toxic to podocyte integrity.	Foot process effacement is **diffuse and global.** Sclerosis is focal & segmental.
Secondary FSGS	Adaptive injury (hyperfiltration damage).	Foot process effacement is **focal and segmental.** Glom & tubular hypertrophy.
Familial FSGS	Genetic defects of podocyte and slit-pore proteins.	Variable depending on affected gene.

For trials of TPE and other therapies, important to ensure subjects have primary FSGS.

FSGS is a group of diseases

	Etiology/ mechanism
Primary FSGS	Circulating factors toxic to podocyte integrity.
Secondary FSGS	Adaptive injury (hyperfiltration damage).
Familial FSGS	Genetic defects of podocyte and slit-pore proteins.

Predict
- recurrence in transplant
- response to TPE

Predict
- no recurrence in transplant
- no response to TPE

Glomerular Permeability Factors in FSGS

Glomerular permeability factors – candidate molecules

- Small, highly glycosylated, hydrophobic protein(s) / peptide(s), 30 to 50 kDa, poorly characterized.
- suPAR (soluble urokinase-type Plasminogen Activator Receptor).
- CLC1 (Cardiotrophin-like cytokine 1).
- others

Glomerular Permeability Factors in FSGS

Candidate molecule:
Small, highly glycosylated, hydrophobic protein 30 to 50 kDa

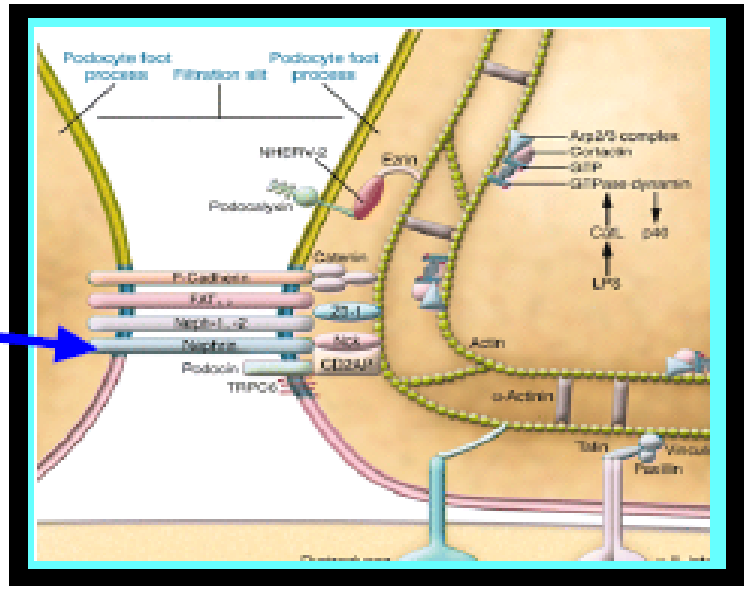
- Poorly characterized because it disintegrates in vitro. (1)
- Permeability activity is decreased by plasmapheresis. (2)
- Proteinuric effect inhibited by galactose (3), but clinical benefit in FSGS patients given oral galactose (4, 5) now disproven.
- The GVV (Glomerular Volume Variability) assay – test plasma dripped on to cultured glomeruli as a biological assay of factor activity.

(1) Savin VJ, et al. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. N Engl J Med 334:878-883, 1996
(2) Savin VJ, McCarthy ET, Sharma M. Permeability factors in focal segmental glomerulosclerosis. Semin Nephrol 23:147-60, 2003
(3) Savin V, et al. Transl Res 151:288-292, 2008
(4) De Smet E, et al. Nephrol Dial Transplant 24:2938-2940, 2009
(5) Kopac M, et al. Ther Apher Dial 15:269-272, 2011

Glomerular Permeability Factors in FSGS

Candidate molecule:
CLC1 (Cardiotrophin-like cytokine 1)

- CLC1 is in IL-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.



McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol 5:2115-2121, 2010*

Glomerular Permeability Factors in FSGS

Candidate molecule:
suPAR (soluble urokinase-type Plasminogen Activator Receptor)

2011: Research implicated "suPAR" 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).

Wei C, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med 17:952-960, 2011*

Glomerular Permeability Factors in FSGS

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.

Wei C, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med 17:952-960, 2011*

Glomerular Permeability Factors in FSGS

Further evidence for a 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.)

Wei C et al. Circulating suPAR in two cohorts of primary FSGS.
J Am Soc Nephrol 23:2051-2059, 2012

Glomerular Permeability Factors in FSGS

Contradictatory evidence for a pathogenic role of suPAR

Bock ME et al. Serum soluble urokinase-type receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. *Clin J Am Soc Nephrol 8:1304-1311, 2013.*

Franco-Palacios CR, et al. Urine but not serum soluble urokinase receptor(suPAR) may identify cases of recurrent FSGS in kidney transplant candidates. *Transplantation 96:394-399, 2013*

Meijers B et al. The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis. *Kidney Int 85:636-640, 2014*

Wada T, et al. A multicenter cross-sectional analysis study of circulating soluble urokinase receptor in Japanese patients with glomerular disease. *Kidney Int 85:641-648, 2014*

Cathelin D, et al. Administration of recombinant soluble urokinase receptor per se is not sufficient to induce podocyte alterations and proteinuria in mice. *JASN 25:1662-1668, 2014*

Harita Y, et al. Decreased glomerular filtration as the primary factor of elevated circulating suPAR levels in FSGS. *Pediatr Nephrol 29:1553-1560, 2014*

ΤΕΛΙΚΟ ΠΡΟΓΡΑΜΜΑ

18ο Πανελλήνιο Συνέδριο Νεφρολογίας

ΑΙΘΟΥΣΑ Β

ΤΕΤΑΡΤΗ 14 ΜΑΪΟΥ 2014

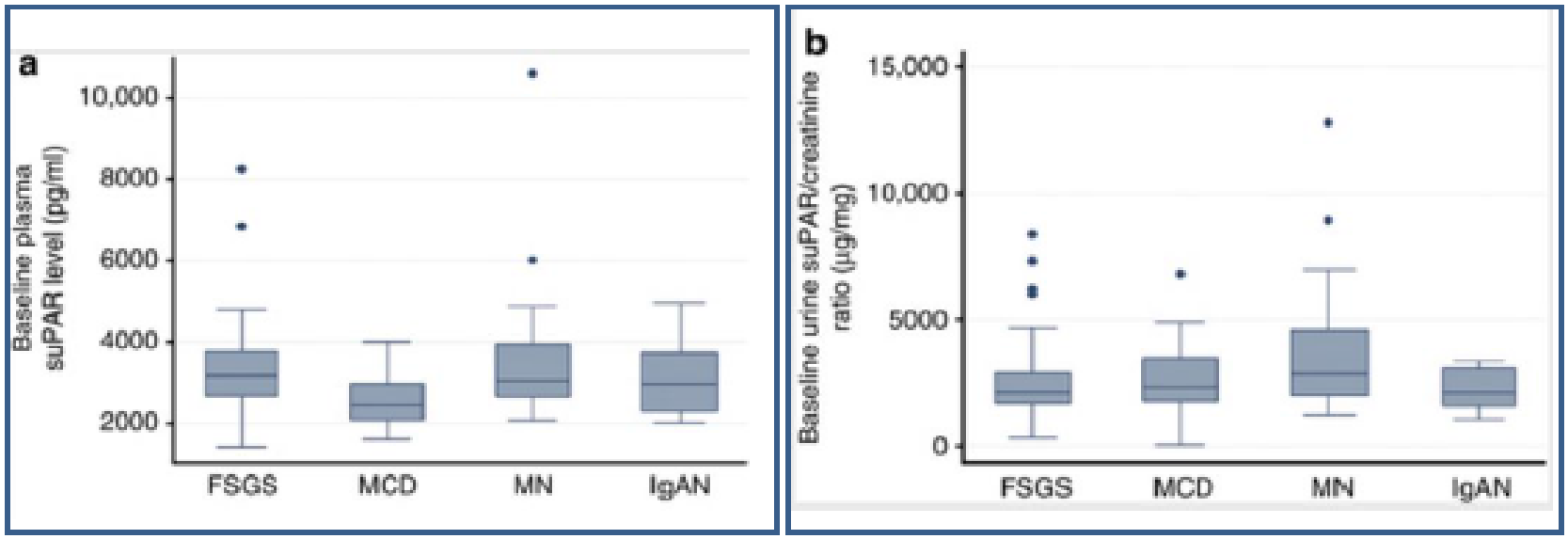
Ο 18 **ΔΙΑΛΥΤΟΣ ΥΠΟΔΟΧΕΑΣ ΠΛΑΣΜΙΝΟΓΟΝΟΥ ΟΥΡΟΚΙΝΑΣΗΣ (SUPAR): ΕΝΑΣ ΥΠΟΣΧΟΜΕΝΟΣ ΔΕΙΚΤΗΣ ΦΛΕΓΜΟΝΗΣ**

Ι. Γριβέας, Χ. Ανδριόπουλος, Ν. Μπακιρτζή, Α. Δράκου

Μονάδα Χρόνιας Αιμοκάθαρσης "Νεφροιατρική"

Glomerular Permeability Factors in FSGS

suPAR: 241 patients from the NEPTUNE observational study



"After adjusting for baseline suPAR concentration, age, gender, proteinuria, and time, the change in suPAR from baseline was associated with eGFR, but this association was not different for patients with FSGS as compared with other diagnoses. Thus these results do not support a pathological role for suPAR in FSGS."

Spinale JM et al. A reassessment of soluble urokinase-type plasminogen activator receptor in glomerular disease. *Kidney Int 87: 564-574, 2015*

Indications for TPE for FSGS

TPE for post-transplant recurrence:

- TPE is 1st-line therapy (plus mycophenolate, cyclophosph or rituximab).
- ASFA (2013) recommendation:
  - TPE daily x 3 days, then 3+/per wk for the next 2 wks.
  - Then 2 - 3/wk until remission (monitoring urine protein quantitation and serum creatinine); can take weeks to months. (1, 2)
- Case Series:
  - 17 TPE treatments in each of 7 adults, all with functioning transplants 10 months later. (3)
  - Remission rates of 80% in adults (4)
  - Remission rate of 88% in children. (5)

(1) Schwartz J, Winters JL, Padmanabhan A, et al. J Clin Apher 28:145-284, 2013
(2) Sanchez AP and Ward DM, Semin Dialysis 25:119-131, 2012
(3) Valdivia P, et al. Transplant Proc 37:1473-1474, 2005
(4) Moroni G, et al. Transpl Int 23:208-216, 2010
(5) Gonzalez E, et al. Pediatr Transplant 15:495-501, 2011

Indications for TPE 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)

(1) Gohh RY, et al. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. Am J Transplantation 5: 2907-2912, 2005

(2) Gonzalez E, et al. Preemptive plasmapheresis and recurrence of focal segmental glomerulosclerosis in pediatric renal transplantation. Pediatr Transplant 15:495–501, 2011

Indications for TPE 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."

(1) Mitwalli AH. Adding plasmapheresis to corticosteroids and alkylating agents: does it benefit patients with focal segmental glomerulosclerosis? Nephrol Dial Transplant 13:1524–1528, 1998

(2) Feld SM, et al. Plasmapheresis in the treatment of steroid resistant focal segmental glomerulosclerosis in native kidneys. Am J Kidney Dis 32:230–237, 1998

(3) Appel GB and Cattran DC. Treatment of primary FSGS. In "UpToDate" ® online.

What does TPE do for FSGS?

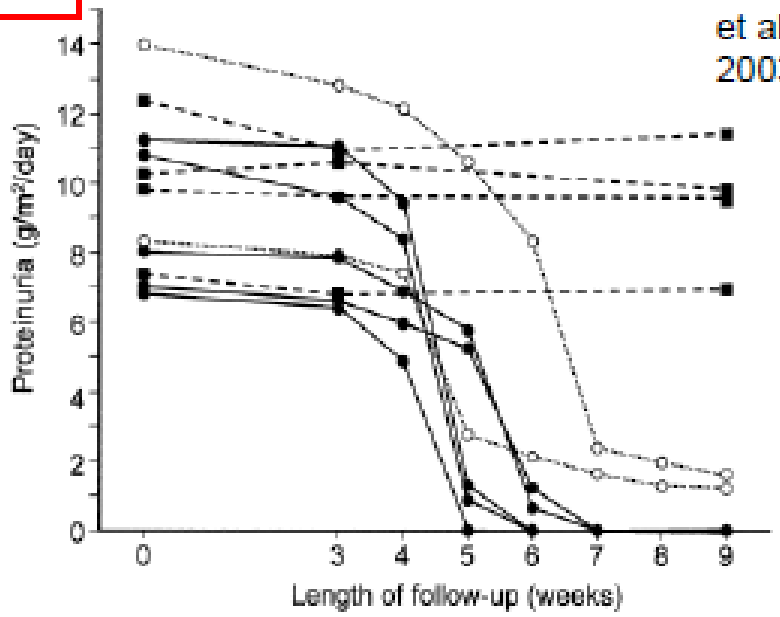
Conventional plasma exchange (with albumin replacement):

- Established first-line treatment for recurrent FSGS (1-9)
- Sometimes useful pre-transplant in primary FSGS
- 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.
  - LDL-cholesterol (and other lipids)

(1) Zimmerman SW: Nephron 40:241-245, 1985
(2) Valdivia P, et al. Transplant Proc 37:1473-1474, 2005
(3) Schachter ME, et al: Clin Nephrol 74:173-181, 2010
(4) Ponticelli C, Glassock RJ: Clin J Am Soc Nephrol 5:2363-2372, 2010
(5) Moroni G, et al. Transpl Int 23:208-216, 2010
(6) Gungor O, et al. Transplant Proc 43:853-857, 2011
(7) Tsagalis G, et al. Artif Organs 35:420-425, 2011
(8) Gonzalez E, et al. Pediatr Transplant 15:495-501, 2011
(9) Wei C, et al. Nature Medicine 17:952-960, 2011

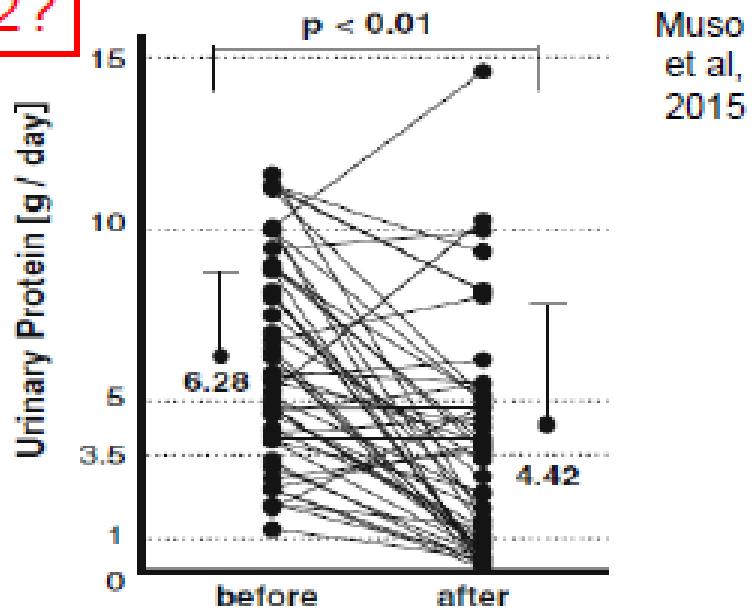
What does LDL-apheresis do for FSGS?

#1?



- Removes Glomerular Permeability factors (as efficiently as TPE)?
- Eliminates nephrotic syndrome in a majority of cases of primary FSGS?

#2?



- Reduces hypercholesterolemia that contributes to glomerular damage?
- Somewhat improves proteinuria in a variety of nephrotic diseases?

LDL Apheresis - systems available worldwide

* = FDA-approved

LDL removal from separated plasma

1. Adsorption
   - Liposorber (Dextran sulfate adsorption) *
   - TheraSorb LDL (Anti-ApoB immunoadsorption)
2. Precipitation
   - H.E.L.P. (Heparin-induced precipitation) *
3. Filtration
   - Double Filtration Plasmapheresis (DFPP)

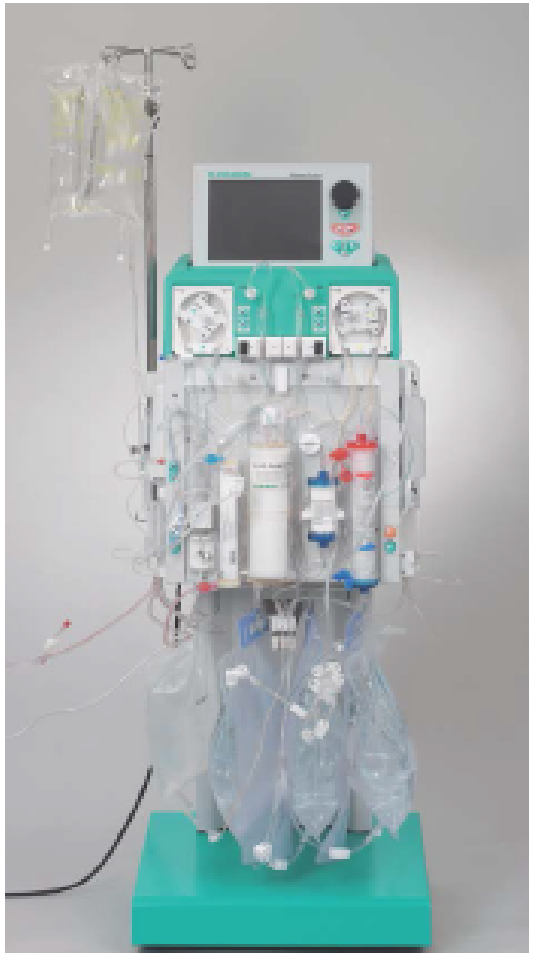
Direct LDL adsorption from whole blood

- Liposorber D (Dextran sulfate adsorption)
- Direct Adsorption of Lipoprotein (DALI) (Polyacrylate adsorption)

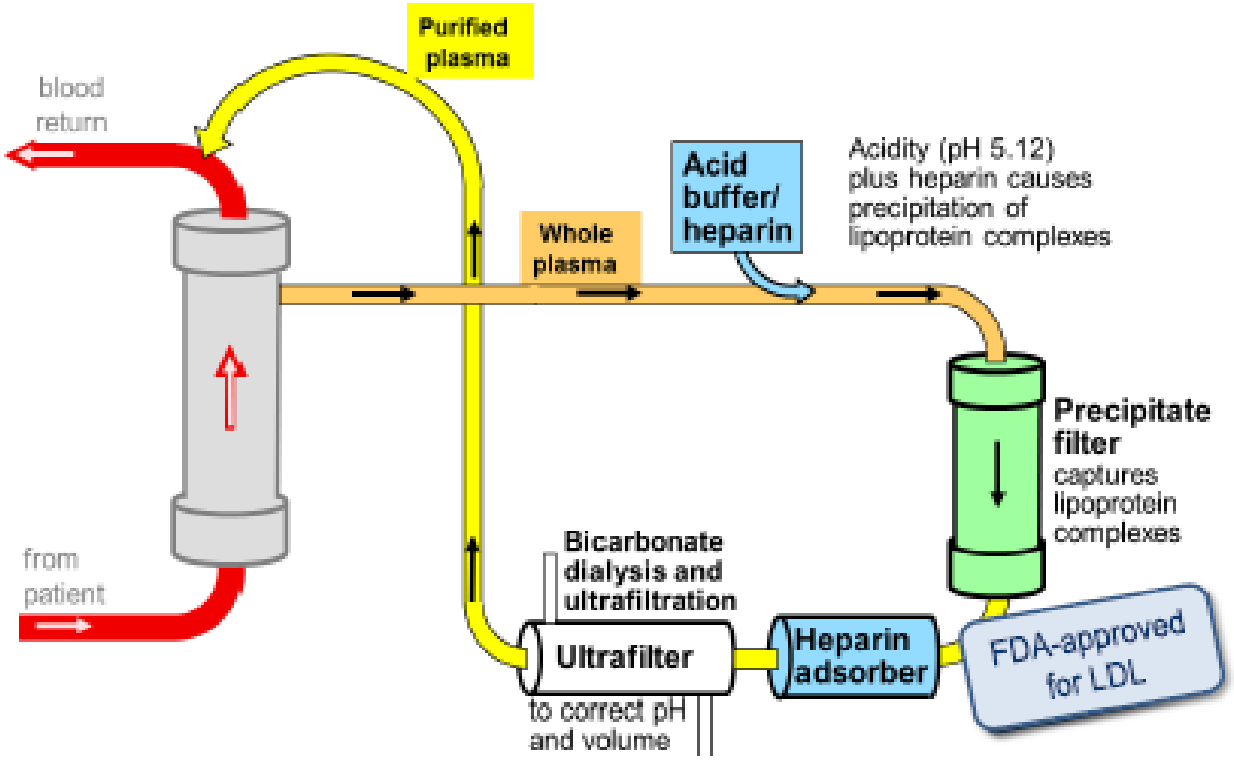
Sanchez AP, Cunard R, Ward DM. The selective therapeutic apheresis procedures. *J Clin Apheresis 28:20-29, 2013*

H.E.L.P. system LDL-Apheresis

B.Braun "Plasmat Futura"®



Heparin-induced Extracorporeal LDL-Cholesterol Precipitation



No evidence - no reported use in FSGS.

Weak evidence for use in FSGS

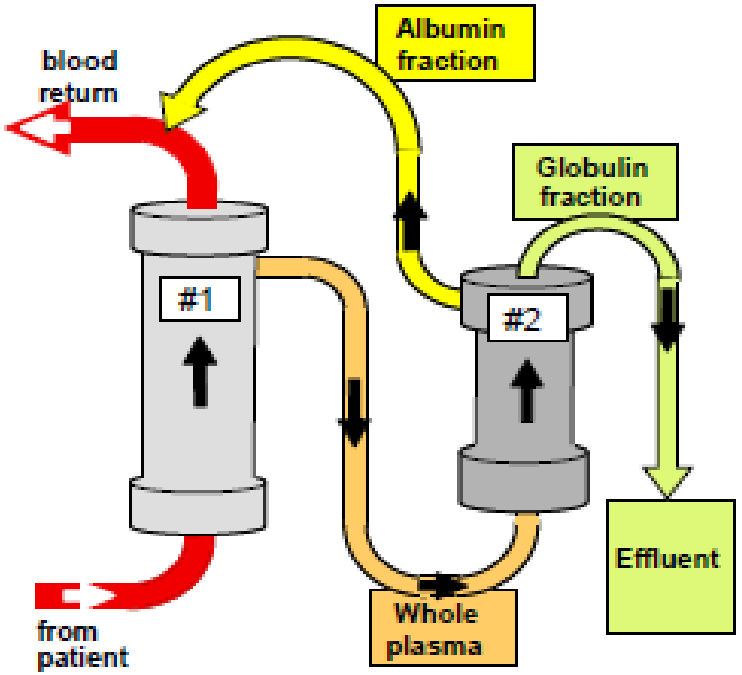
Double-filtration (cascade) plasmapheresis (DFPP):

- Returns albumin (67 kDa) and all smaller molecules to the patient.

#1: Plasma-filter
Pore size: large
Cut-off: >2000 kD

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

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



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

LDL	~3000 kDa
IgM	~ 970 kDa
IgG	~ 140 kDa
Albumin	~ 67 kDa
Permeabilty factors	< 50 kDa

A few DFPP cases reported together with LDL-apheresis cases in FSGS publications.

Weak evidence for use in FSGS

Immunoadsorption (IA):

Anti-IgG columns

- Some reports say effective for recurrent FSGS. (1, 2)
- But they remove IgG, not lipoproteins or small proteins <50 kDa.

  Example: Globaffin ® columns use peptide ligand PGAM146 to adsorb IgG (Fresenius, Germany).
- One case report using Globaffin IA vs TPE claims effectiveness of IA. (3)

(1) Haas M, et al. Nephrol Dial Transplant 13:2013–2016, 1998
(2) Dantal J, Godfrin Y, Koll R, et al: J Am Soc Nephrol 9:1709-1715, 1998
(3) Morath C, et al. Am J Therapeutics 20:226-229, 2013

Weak evidence for use in FSGS

Impression:

- Claims for effectiveness of immunoadsorption (IA) or double-filtration (DFPP) are based on minimal evidence:
  - IA removes IgG but not LDL or proteins <50 kDa.
  - DFPP removes IgG and LDL but not proteins <50 kDa.

Other column adsorption apheresis:

Protein A columns

- Only one report of effectiveness for recurrent FSGS (1)
- Removes IgG, but not LDL or small proteins <50 kDa, etc.

Tryptophan adsorption column:

- One center reports "Effective for steroid resistant FSGS". (2)

(1) Dantal J, Bigot E, Bogers W, et al. N Engl J Med 330:7–14, 1994
(2) Beige J, et al. Am J Transplant 3:1459, 2003

Journal of Clinical Apheresis 31:149–338 (2016)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

Joseph Schwartz,[1] Anand Padmanabhan,[2] Nicole Aqui,[3] Rasheed A. Balogun,[4] Laura Connelly-Smith,[5] Meghan Delaney,[6] Nancy M. Dunbar,[7] Volker Witt,[8] Yanyun Wu,[9] and Beth H. Shaz[1,10,11]*

TABLE II. Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

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TABLE IV. *Continued*

Disease name	TA Modality	Indication	Category	Grade	Page
Familial hypercholesterolemia	LDL apheresis	Homozygotes	I	1A	211
	LDL apheresis	Heterozygotes	II	1A	
	TPE	Homozygotes with small blood volume	II	1C	
Focal segmental glomerulosclerosis	TPE	Recurrent in transplanted kidney	I	1B	213
	LDL apheresis	Steroid resistant in native kidney	III	2C	
Graft-versus-host disease	ECP	Skin (chronic)	II	1B	216
	ECP	Non-skin (chronic)	II	1B	
	ECP	Skin (acute)	II	1C	
	ECP	Non-skin(acute)	II	1C	

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Rationale for therapeutic apheresis

Patients with reccurent FSGS appear to have a permeability factor, which is removed by TPE and decreasing plasma concentration coincides with proteinuria improvement. Pretransplant TPE may prevent or delay recurrence in high-risk patients but this finding has not been universal. Usually TPE is started once recurrence is diagnosed. The number of TPEs needed to control proteinuria, surrogate marker of FSGS, is variable. Garcia (2006) treated 9 children with 10 TPEs plus high doses of cyclosporine, mycophenolate mofetil, and prednisone, starting <48 h after the diagnosis of proteinuria, and reported a 55% complete remission and 12% partial response rates, compared with no remissions among five children who did not receive TPE. Studies support the need for immunosuppression as well as TPE. Sener (2009) reported on four adults treated with 9–15 TPEs of and mycophenolate mophetil who had preserved renal function as late as 34 months post-transplant. A retrospective study of adults with FSGS (Moroni, 2010) suggested that TPE and ACE inhibitors resulted in either complete or partial remission of proteinuria in 80% of patients. Tsagalis (2011) reported 50% complete remission and 50% partial remission in four patients with recurrent FSGS treated with a combination of TPE and rituximab. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and IA with staphylococcal protein A columns.

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Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least six more TPEs in the subsequent 2 weeks. Another reported approach of intense/maintenance TPE treatment includes the following schedule: 3/week for the first 3 week, followed by 2/week for 3 week, 1/week until month 3, 2/month until month 5, and 1/month until month 9, with concomitant immunosuppression treatment. Usually proteinuria decreases gradually while the patient is being treated with TPE as well as the creatinine, in those patients who showed decreased renal clearance at diagnosis of FSGS recurrence. Tapering should be decided on a case by case basis and is guided by the degree of proteinuria. Timing of clinical response is variable and complete abolishment of proteinuria may take several weeks to months. Some patients require long-term regimens of weekly to monthly TPEs to prevent reappearance of the proteinuria. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE. It is recommended that TPE be instituted as soon as recurrent FSGS is diagnosed, in order to halt the process and maintain kidney function.

Kidney Res Clin Pract 31 (2012) 205–213

Kidney Research and Clinical Practice

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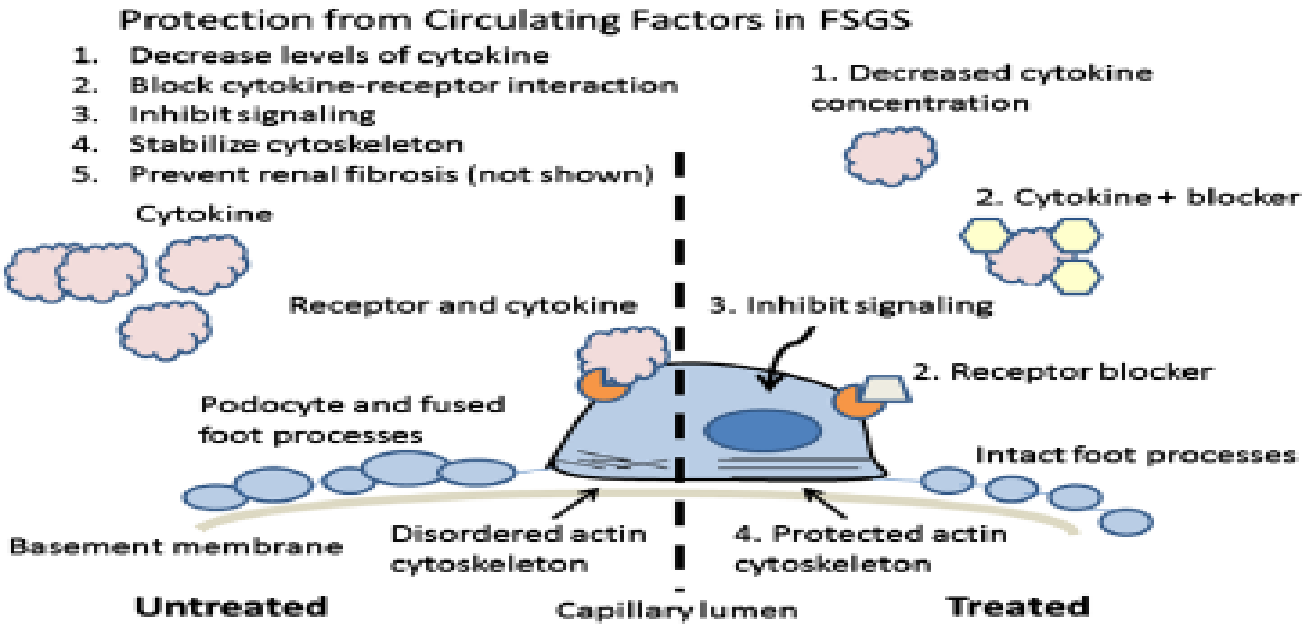
Contents lists available at ScienceDirect

Review article

Permeability factors in nephrotic syndrome and focal segmental glomerulosclerosis

Virginia J. Savin*, Ellen T. McCarthy, Mukut Sharma

Kansas City Veterans Administration Medical Center, Kansas City, MO, United States



FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence: 7/1,000,000	Indication	Procedure	Recommendation	Category
	Recurrent in transplanted kidney	TPE	Grade 1B	I
	Steroid resistant in native kidney	LDL Apheresis	Grade 2C	III

No. of reported patients: >300	RCT	CT	CS	CR
Recurrent in transplanted kidney	0	3(48)	49(224)	15(17)
Steroid resistant in native kidney	0	0	1(11)	4(4)

Description of the disease

Focal segmental glomerulosclerosis (FSGS) is a histologically characteristic finding in renal biopsy specimen characterized by focal areas of sclerosis of some glomeruli adjacent to other intact glomeruli. Several FSGS histological variants (cellular, collapsing, tip lesion, perihilar, and not otherwise specified) exist, which have different clinical presentations and treatment response. 80% of FSGS cases are idiopathic. Other causes include mutations in specific podocyte genes, secondary to drugs, and hemodynamic adaptive response. Idiopathic FSGS is postulated to result from a plasma factor or factors of unknown origin that injure(s) the filtration barrier and/or increases glomerular permeability. This hypothesis is supported by the observation that FSGS may recur in a renal allograft. Inconsistent data favor a permeability factor, thought to be suPAR, a membrane bound receptor for uPA (unknown), circulates as multiple fragments of different sizes. ESRD occurs within 3–7 years. Recurrence occurs in up to 40% of renal allografts. Idiopathic FSGS poses the highest risk of recurrence post-transplant. Other risk factors for recurrence are younger age, short duration of native kidney disease, history of recurrence with previous transplant, heavy proteinuria, bilateral native nephrectomy, race, and living donor kidney. FSGS recurrence can happen a few hours to 2 years post-transplant. Recurrent FSGS in the transplanted kidney is diagnosed histologically or when nephrotic range proteinuria develops. If untreated, recurrent FSGS will ultimately lead to permanent graft loss within months. Those who lost grafts to recurrence have >80% chance of recurrent FSGS in subsequently transplanted kidneys.

Current management/treatment

Patients with primary FSGS with proteinuria >3 g/day do not benefit from TPE and are treated with corticosteroids. For secondary FSGS, underlying cause should be treated. The main goal of recurrent FSGS treatment is to achieve complete or partial remission of proteinuria and prevent premature allograft loss. Even though the use of TPE in treating FSGS in native kidneys has been disappointing, treatment for recurrent FSGS often responds to a combination of TPE, high dose corticosteroids, other immunosuppressives, and/or angiotensin II receptor antagonist (ARB) or ACE inhibitor. More recently, rituximab, IVIG, and mycophenolate mofetil have also been used in conjunction with TPE.

Rationale for therapeutic apheresis

Patients with recurrent FSGS appear to have a permeability factor, which is removed by TPE and decreasing plasma concentration coincides with proteinuria improvement. Pretransplant TPE may prevent or delay recurrence in high-risk patients but this finding has not been universal. Usually TPE is started once recurrence is diagnosed. The number of TPEs needed to control proteinuria, surrogate marker of FSGS, is variable. Garcia (2006) treated 9 children with 10 TPEs plus high doses of cyclosporine, mycophenolate mofetil, and prednisone, starting <48 h after the diagnosis of proteinuria, and reported a 55% complete remission and 12% partial response rates, compared with no remissions among five children who did not receive TPE. Studies support the need for immunosuppression as well as TPE. Sener (2009) reported on four adults treated with 9–15 TPEs of oral mycophenolate mophetil who had preserved renal function as late as 34 months post-transplant. A retrospective study of adults with FSGS (Maroni, 2010) suggested that TPE and ACE inhibitors resulted in either complete or partial remission of proteinuria in 80% of patients. Tsagalis (2011) reported 50% complete remission and 50% partial remission in four patients with recurrent FSGS treated with a combination of TPE and rituximab. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and IA with staphylococcal protein A columns.

Technical notes

Vascular access may be obtained through arteriovenous fistulas or grafts used for dialysis.

Volume treated: 1–1.5 TPV	Frequency: Daily or every other day
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least six more TPEs in the subsequent 2 weeks. Another reported approach of intense/maintenance TPE treatment includes the following schedule: 3/week for the first 3 week, followed by 2/week for 3 week., 1/week until month 3., 2/month until month 5, and 1/month until month 9., with concomitant immunosuppression treatment. Usually proteinuria decreases gradually while the patient is being treated with TPE as well as the creatinine, in those patients who showed decreased renal clearance at diagnosis of FSGS recurrence. Tapering should be decided on a case by case basis and is guided by the degree of proteinuria. Timing of clinical response is variable and complete abolishment of proteinuria may take several weeks to months. Some patients require long-term regimens of weekly to monthly TPEs to prevent reappearance of the proteinuria. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE. It is recommended that TPE be instituted as soon as recurrent FSGS is diagnosed, in order to halt the process and maintain kidney function.

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