FSGS: Insights and Novel Treatment Perspectives

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University of Ioannina

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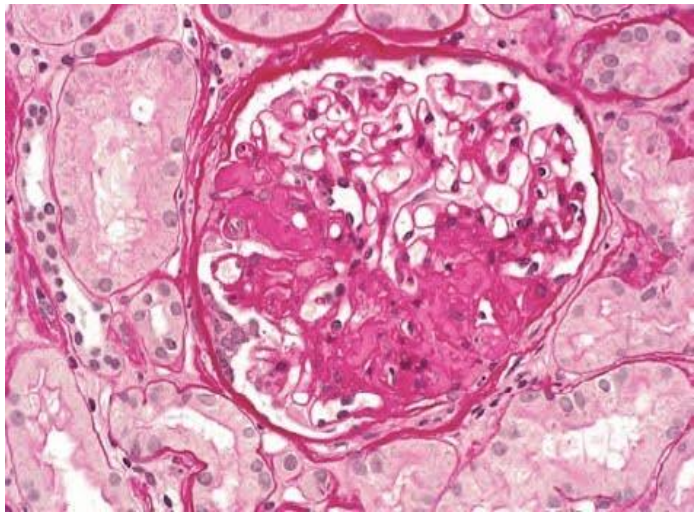
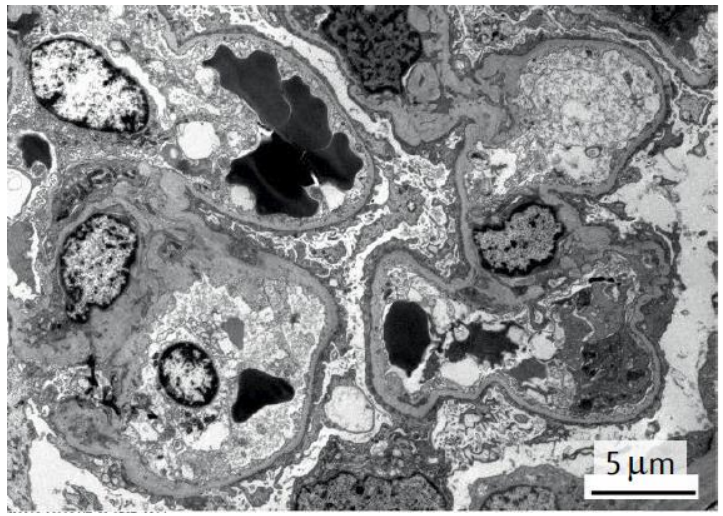
Patient #1

- A Caucasian female, 23 years old with abrupt onset of full nephrotic syndrome:

  - ✓ approx. 10 kg increase in body weight
  - ✓ 24h urine protein 12g/day
  - ✓ Total protein 38 g/l
  - ✓ Serum Albumin 15 g/l





LM: 21 Glomeruli. 1 globally sclerotic and 5 FSGS. Diffuse and severe tubular degenerative changes. No interstitial fibrosis

EM: complete FPE

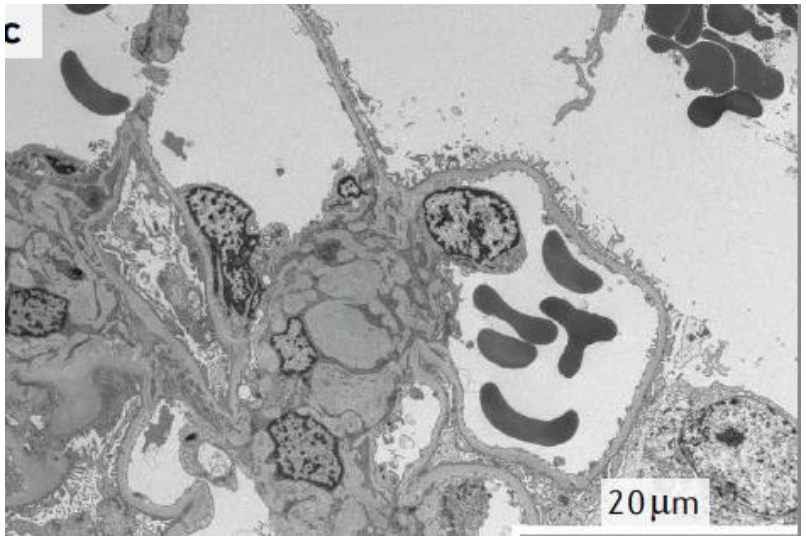
Patient #2

- A Caucasian male, 28 years old with:

✓24h urine protein 6g/day

✓Normal total protein and serum albumin

✓No edema, increased BP (150/100mmHg)



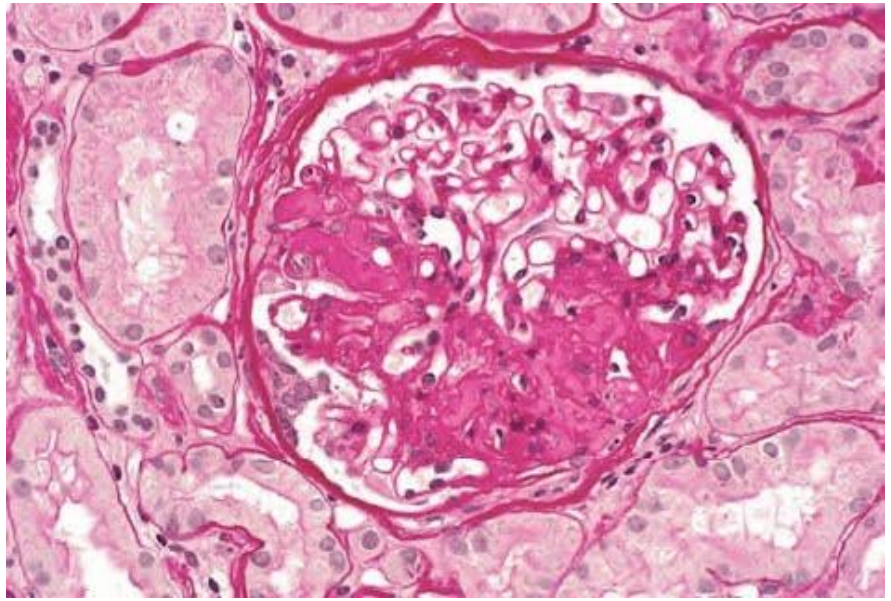
- **Light microscopy: 18 glomeruli: 2 global sclerotic and 3 with FSGS**
- **Electron Microscopy:** partial FPE

→Primary FSGS

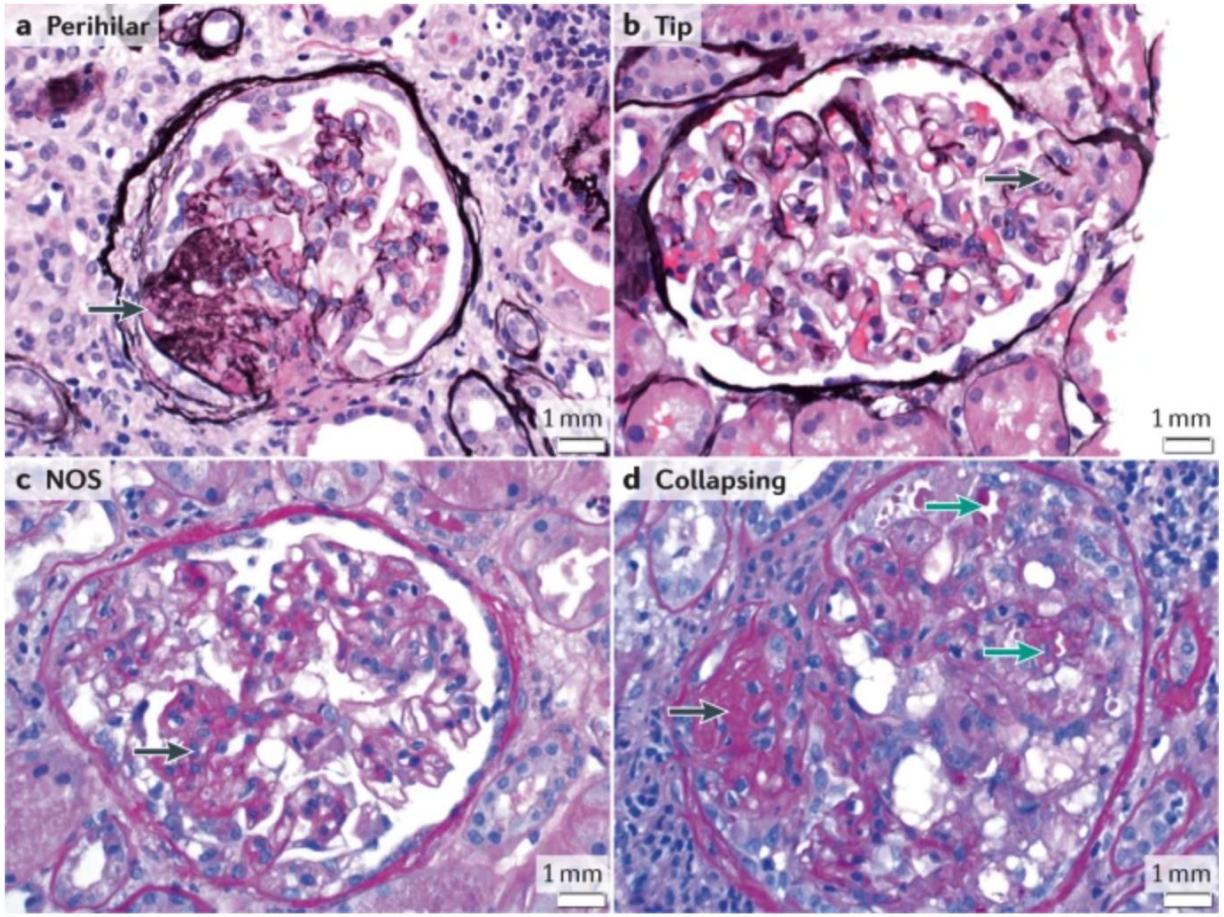
Are these patients the same?

FSGS

- FSGS is a **lesion** and not a disease
- It can be a result of a wide array of pathogenic processes
- It cannot be purely diagnosed based on histology.

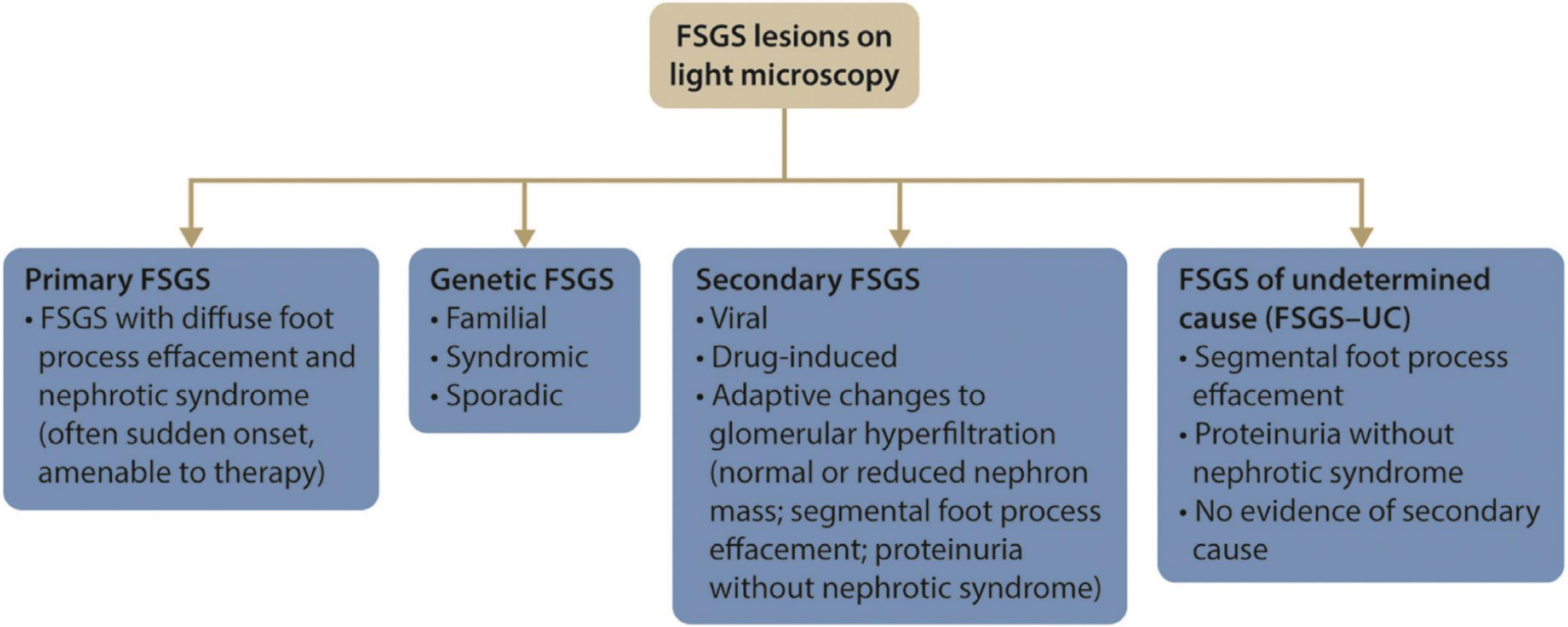


Does the histological subtype have prognostic relevance?

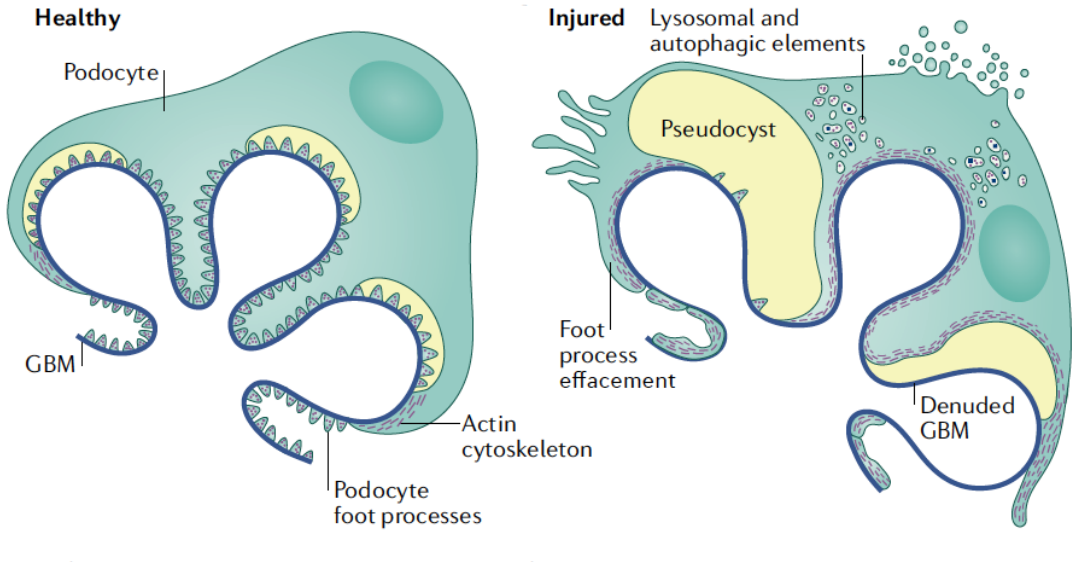


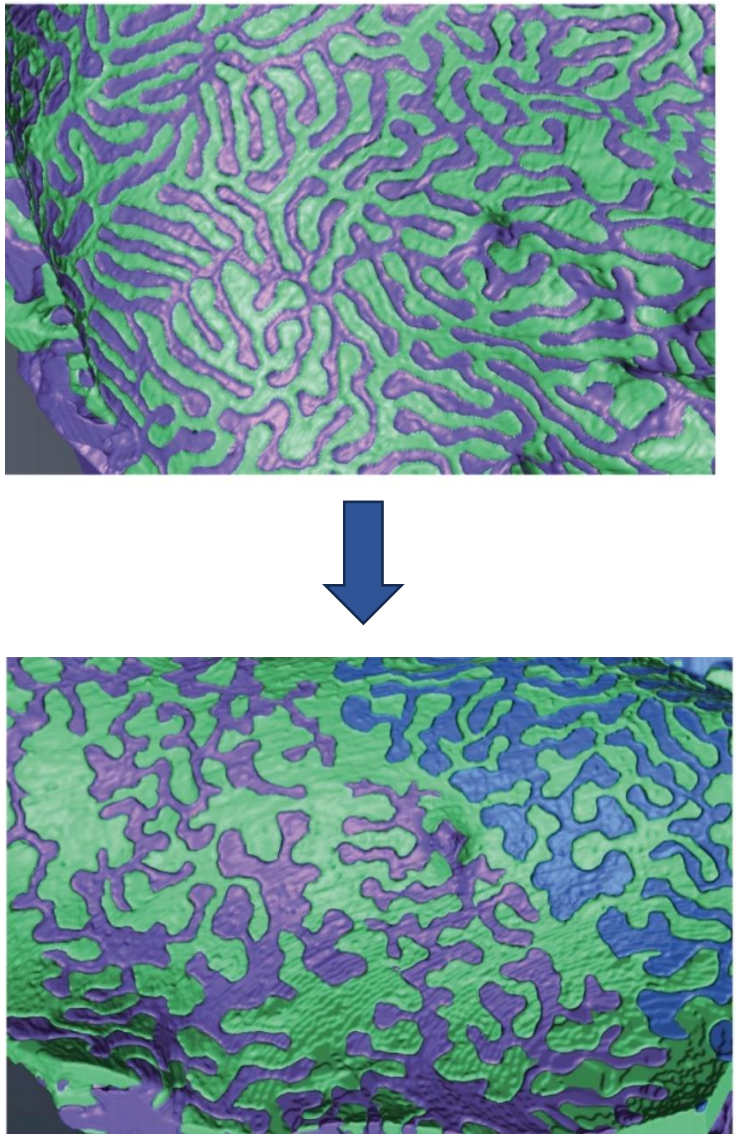
D'Agati VD Am. J. Kidney Dis. ***43****, 368–382 (2004).*

Classification of FSGS



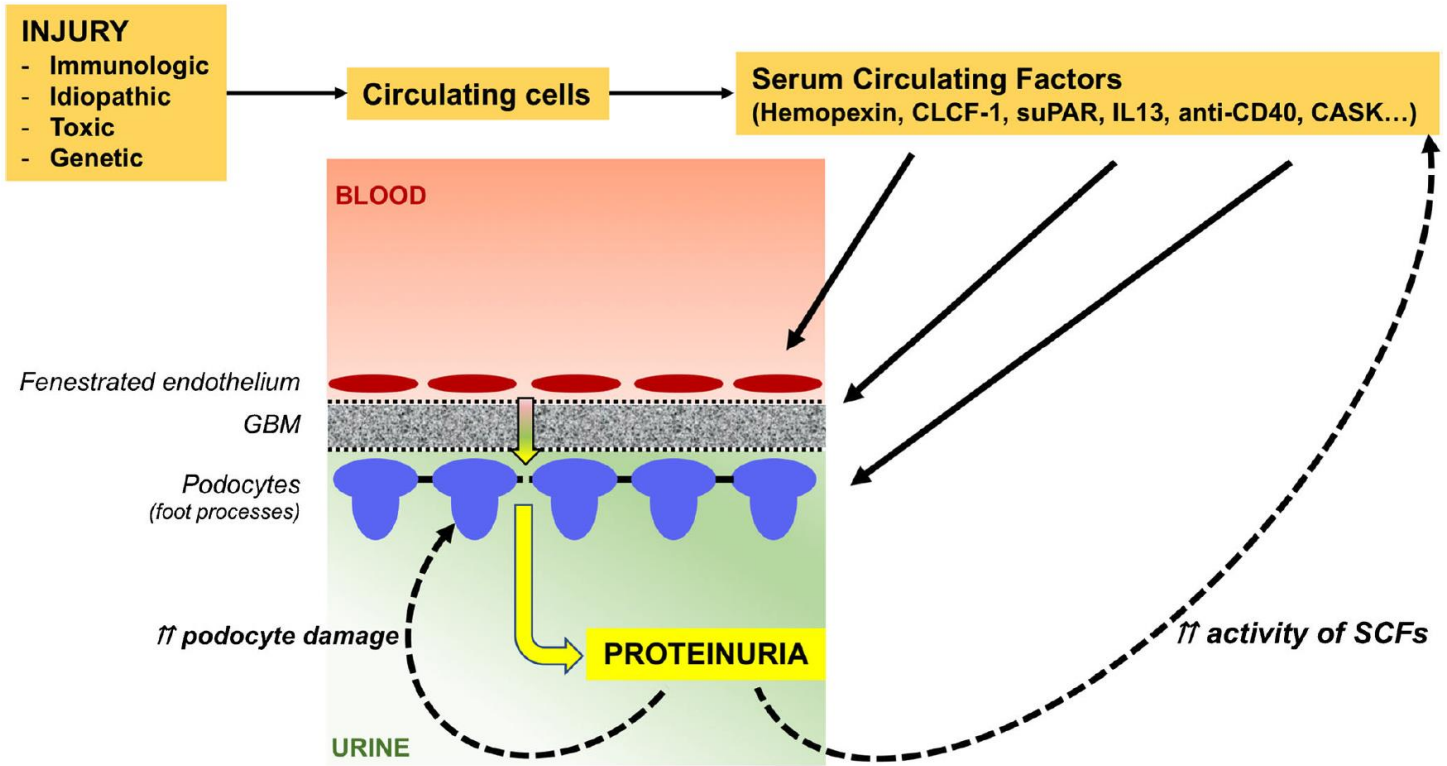
Mechanisms of podocyte injury





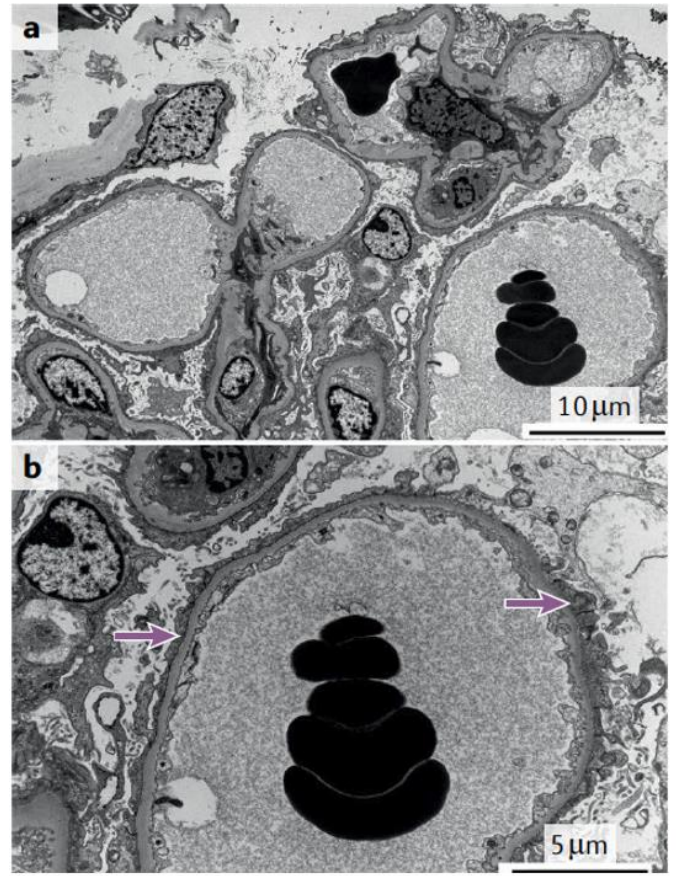
De Vriese AS Nat Rev Nephrol. 2021 Sep

Primary FSGS = ppfFSGS



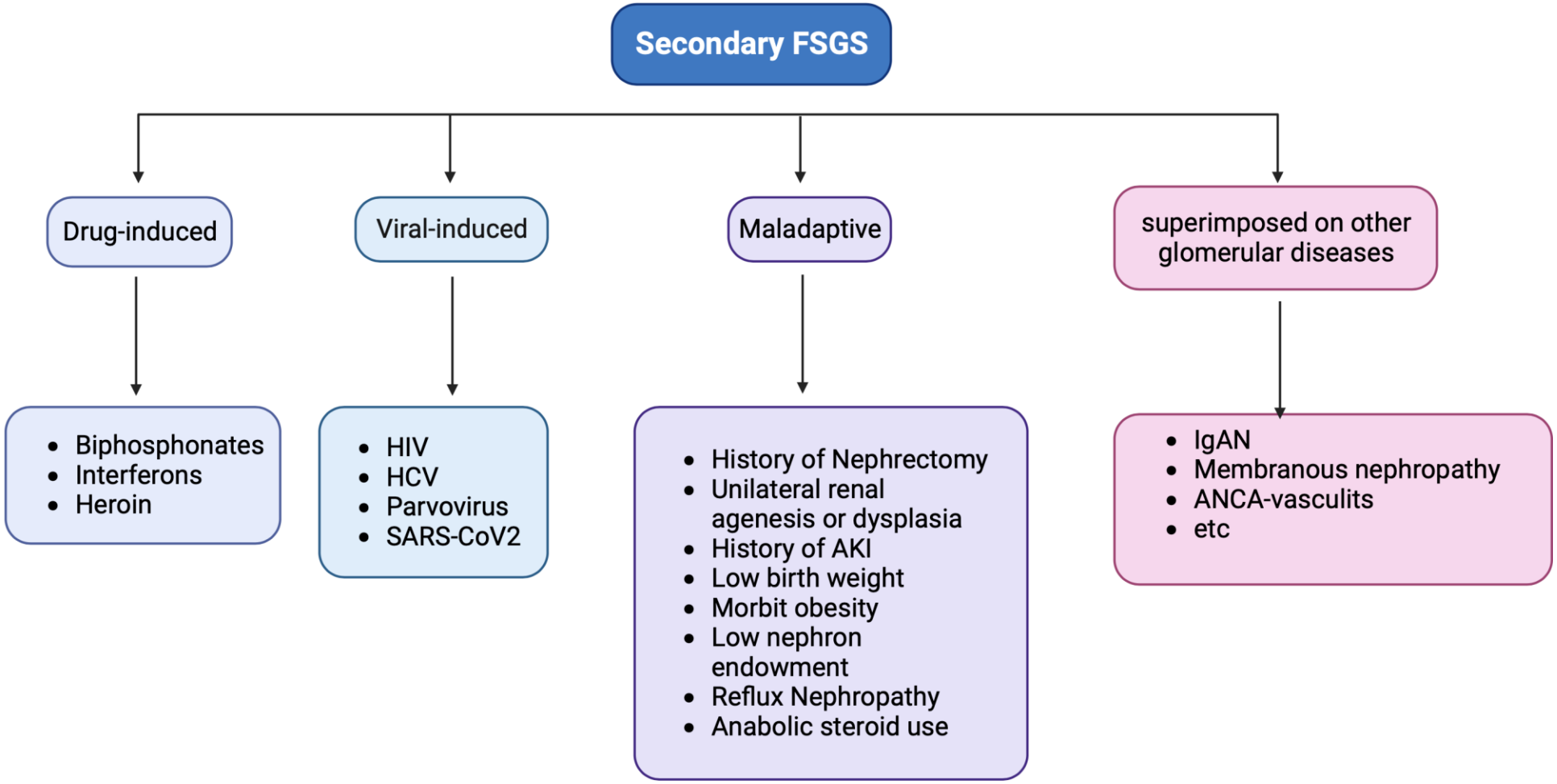
Candelier et al. Cell and Tissue Research 2019

Affects <u>ALL</u> podocytes Diffuse FPE on EM



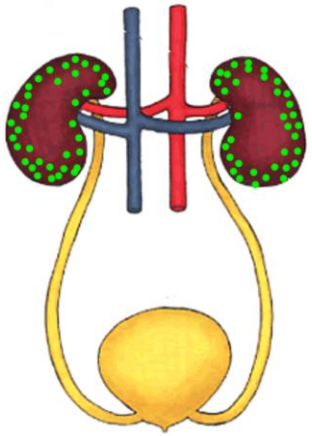
Podesta M and Ponticelli C, Front Med. 2020

Secondary FSGS



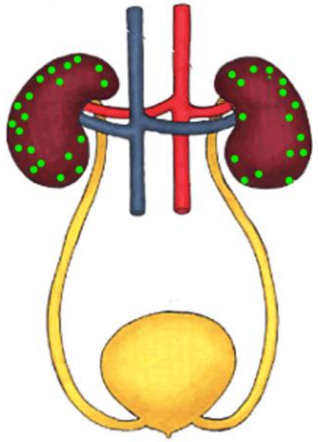
Maladaptive FSGS

Increase in total kidney GFR

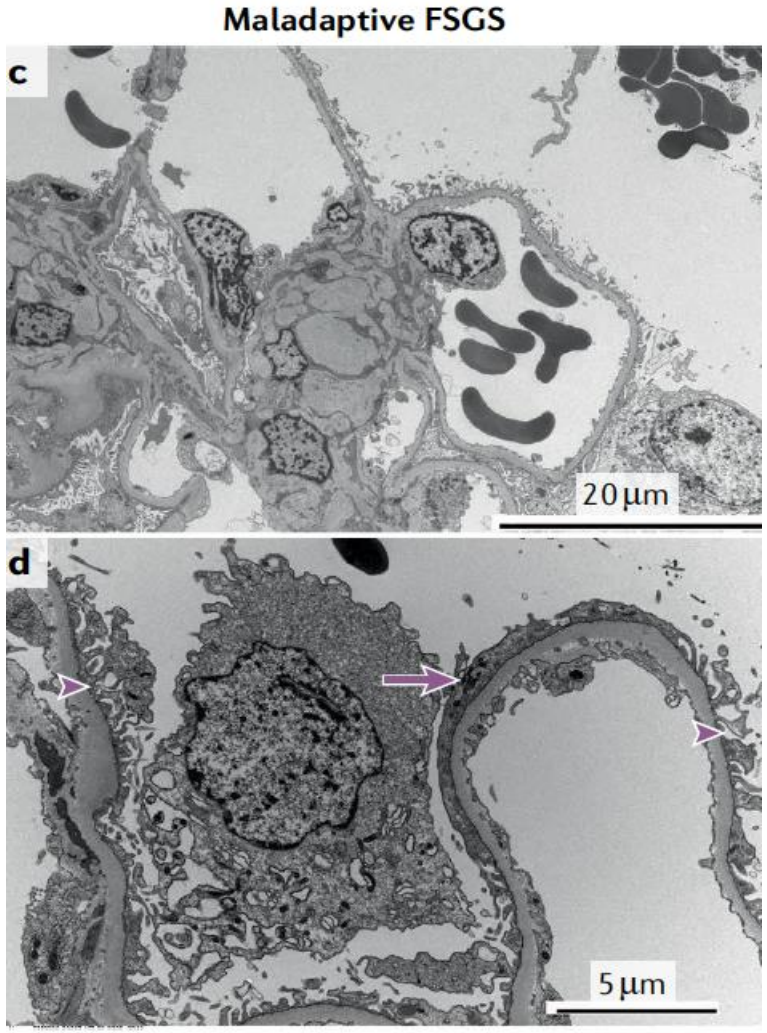


- ✓ congenital cyanotic heart disease
- ✓ sickle cell anemia
- ✓ obesity
- ✓ androgen abuse
- ✓ sleep apnea
- ✓ high-protein diet.

Reduced renal mass



- ✓ prematurity and/or small for gestation age
- ✓ renal anomalies,
- ✓ reflux nephropathy
- ✓ AKI.



Rosenberg AC, Clin J Am Soc Nephrol. 2017

Genetic FSGS

Table 1 | **Genes implicated in FSGS**

Function of the gene product	Gene
Slit diaphragm proteins	*NPHS1, NPHS2, CD2AP, CRB2, TRPC6, FAT1*
Actin binding	*PLCE1, ACTN4, MYO1E, MYH9, INF2, ANLN, AVIL*
Actin regulation	*ARHGDIA, ARHGAP24, KANK1, KANK2, KANK4, MAGI2, DLC1, ITSN1, ITSN2, DAAM2*
Nuclear transcription factors	*LMX1B, WT1, SMARCAL1, NXF5*
Nuclear pore complex proteins	*NUP93, NUP85, NUP107, NUP133, NUP160, NUP205, XPO5*
Mitochondrial proteins	*COQ2, COQ6, COQ8B (ADCK4), PDSS2, MTTL1*
KEOPS complex (tRNA modification)	*OSGEP, TP53RK, TPRKB, LAGE3*
Lysosomal proteins	*SCARB2*
Adhesion proteins	*ITGA3, ITGB4, LAMB2*
Glomerular basement membrane proteins	*COL4A3, COL4A4, COL4A5, COL4A6, LAMA5*
Other	*SGPL1, CUBN, PTPRO, WDR73, EMP2, DGKE, ALG1*

respond to CNIs

respond to CNIs

respond favourably to RASi

Ashraf S. et al Nat. Commun. 2018 May 17;9(1):1960.
Malakasioti, G., Pediatr. Nephrol. 2020
Daina, E. et al. Nephron 2015

Genetic FSGS

- Common in infants and young children; up to 60% of children with SRNS
- Large gene panels or whole exon sequencing can detect potentially pathogenic mutations in as many as 30% of adults with FSGS lesions
- Proteinuria is variable
- Most adult patients with persistent moderate-to-severe proteinuria progress to kidney failure, at variable rates

Genetic FSGS: When should be considered?

- ✓Mismatch between clinical presentation and EM findings
- ✓Looks like maladaptive FSGS but not cause can be identified
- ✓Appears as primary FSGS but fails to respond to therapy

Patient #1

- A Caucasian female, 23 years old with abrupt onset of full nephrotic syndrome
  - ✓ ca. 10 kg increase in body weight
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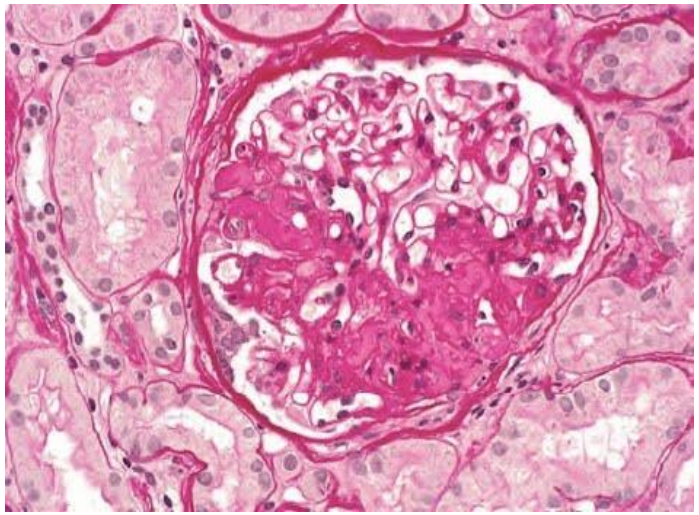
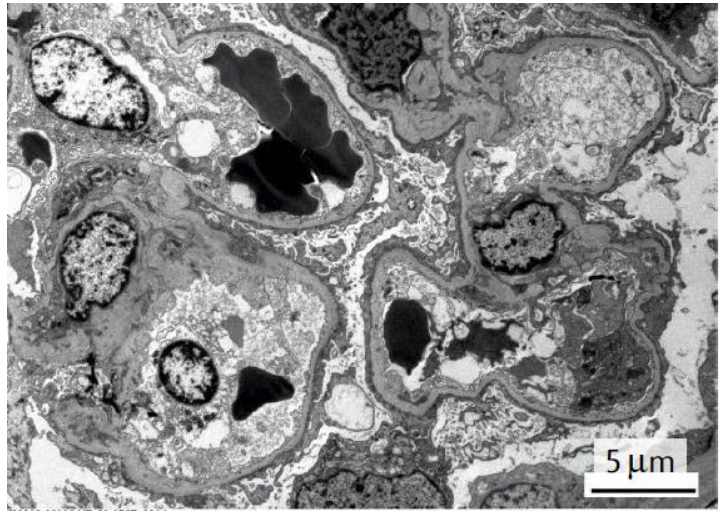
  - ✓ Serum Albumin 15 g/l
  - ✓ Cholesterin 327 mg/dl



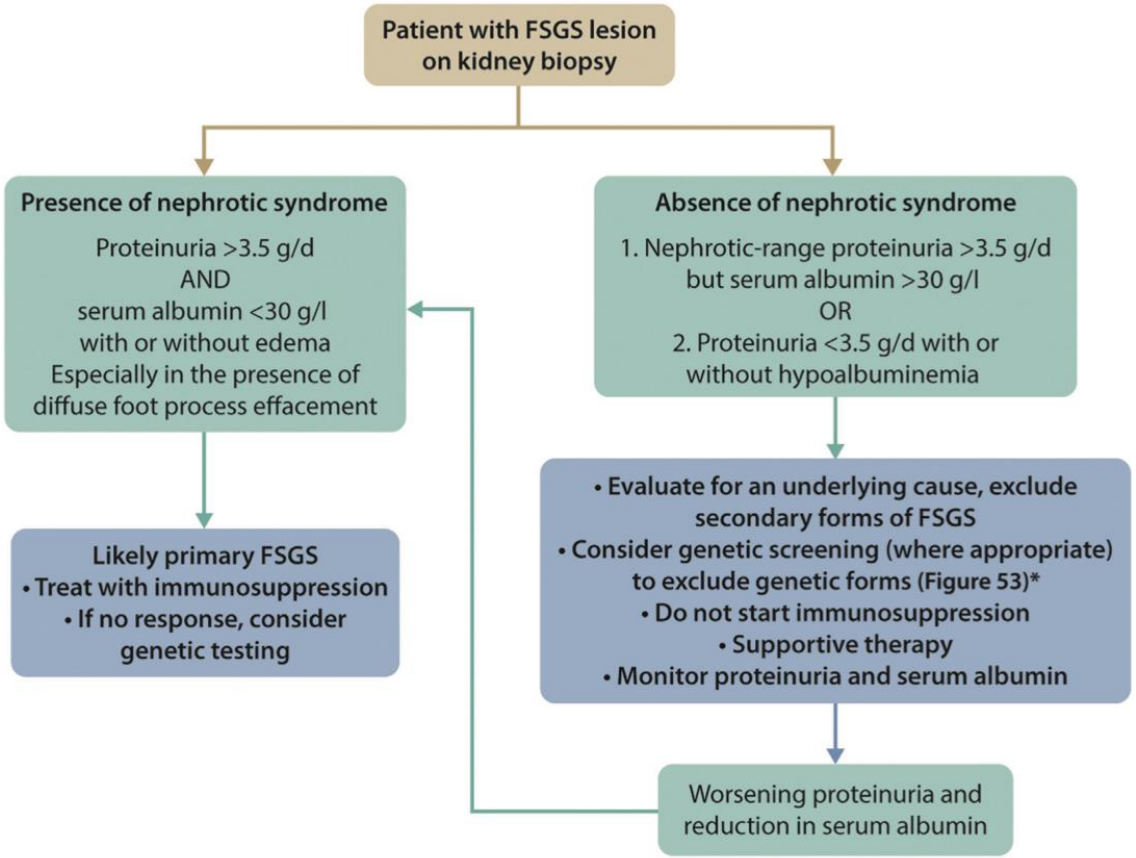


Biopsy: 21 Glomeruli. 5 FSGS EM: diffuse FPE

Approach to treatment with ppfFSGS

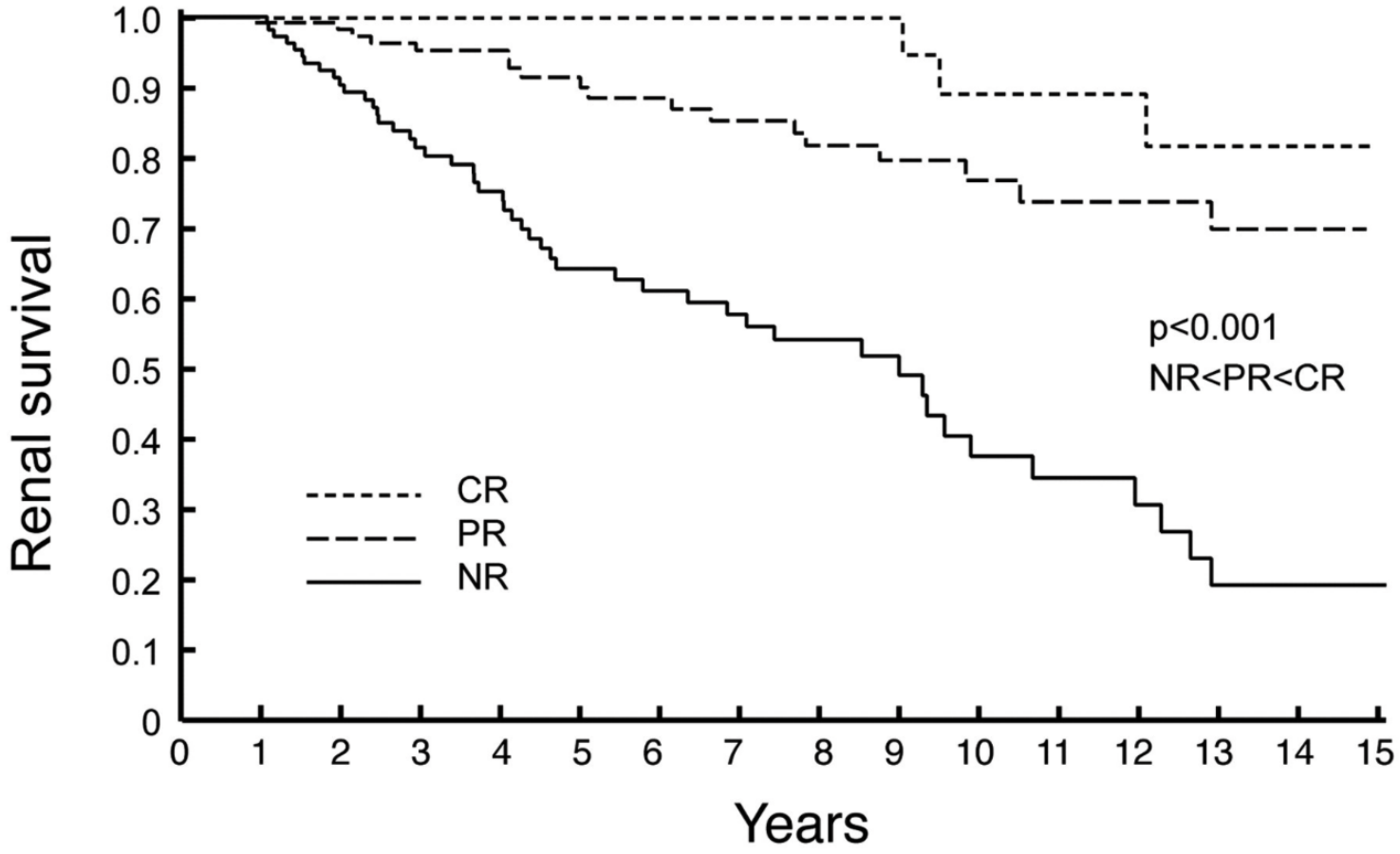
Immunosuppression

- Initial immunosuppression remains high dose steroids
- Strongest existing data
- Treatment response helps support/refute classification of permeability factor mediated



Goal of treatment: ppfFSGS

Study cohort 281 nephrotic FSGS patients



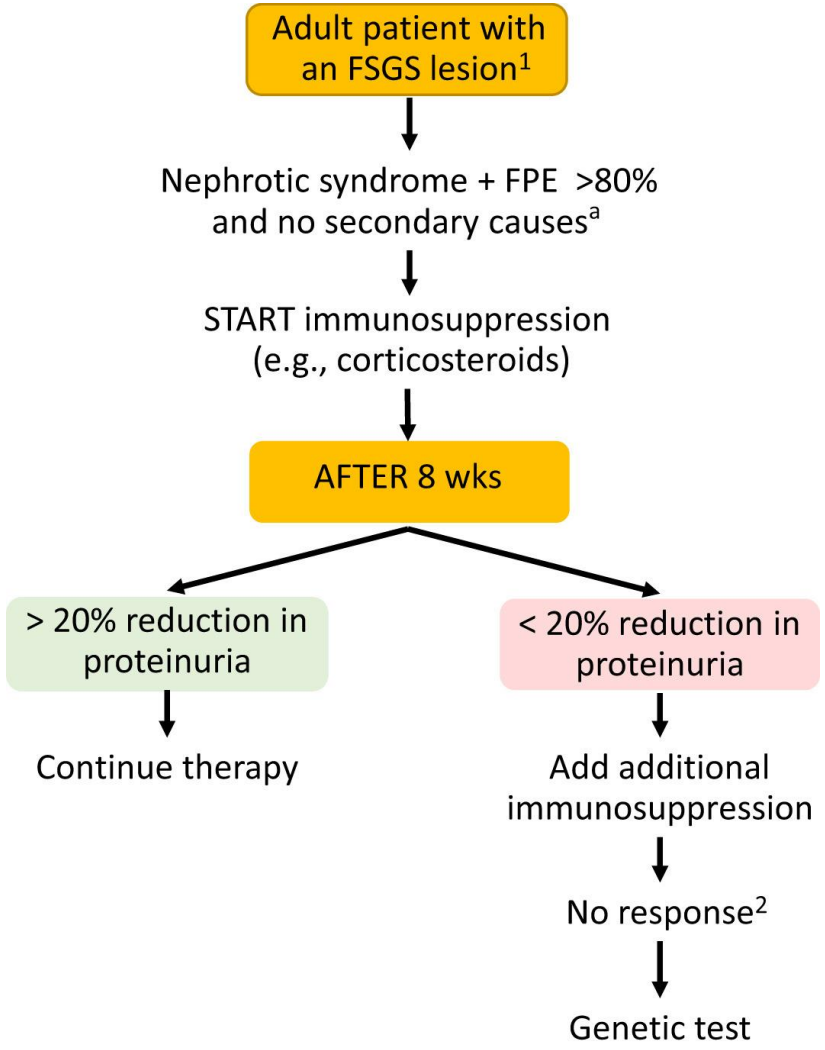
Troyanov S et al. JASN 2005;16:1061-1068

Steroid treatment in FSGS-how much and how long?

- Retrospective anaylsis of cohort of 70 FSGS patients considered to be ppfFSGS treated with high dose steroids

✓20% or more reduction in proteinuria at week 8→strong predictor of response (partial or complete remission)

✓If less than 20% at 8 weeks highly unlikely to not have any response early steroid withdrawal



Kidney International Reports 2022 79-12DOI: (10.1016/j.ekir.2021.11.021)

MCD and ppFSGS: what is on the horizon?

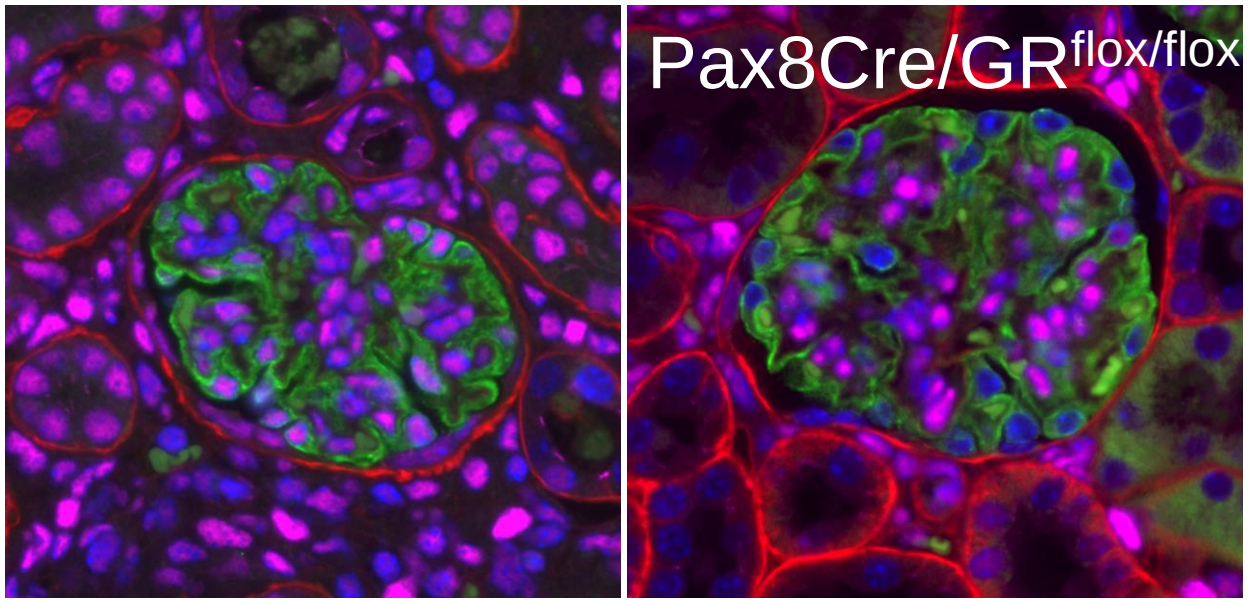
- Targeting the permeability factor(s)
- Suppressing permeability factor formation
- Targeting haemodynamic abnormalities
- Targeting geneting mutations

Table 1. Some recent and ongoing clinical trials in focal segmental glomerulosclerosis

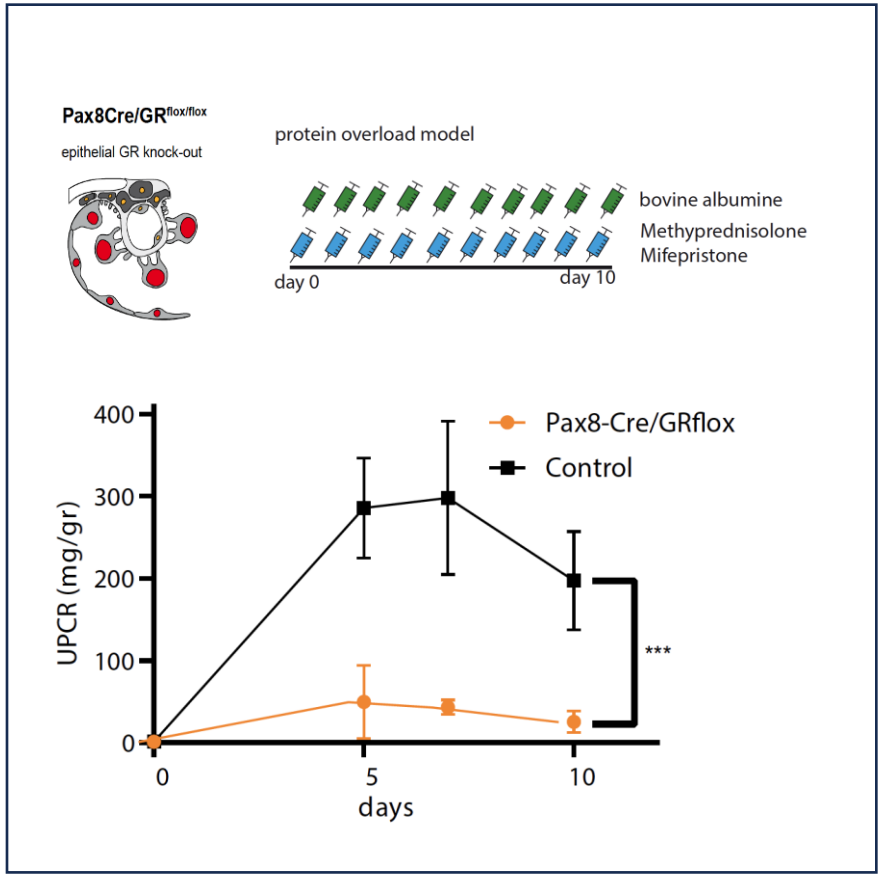
NCT number	Drug	Mechanism of action	Status	Phase	Completion
NCT01613118	Sparsentan	Dual ETA receptor/AT1 receptor antagonist	Active, not recruiting	Phase 2	February 2026
NCT03493685				Phase 3	
NCT05003986			Peds: Recruiting	Phase 2	June 2025
NCT04573920	Atrasentan	Dual ETA receptor/AT1 receptor antagonist	Recruiting	Phase 2	February 2026
NCT03970122	GFB-887	*TRPC5* channel inhibitor	Completed	Phase 1	April 2020
NCT04387448			Recruiting	Phase 2	August 2022
NCT04950114				Phase 2	September 2025
NCT03448692	PF-067301512	*SLIT2* antagonist	Recruiting	Phase 2	August 2025
NCT04340362	VX-147	*APOL1* antagonist	Completed	Phase 2	December 2021
NCT05312879			Recruiting	Phase 2/3	June 2026
NCT05267262	R3R01	Lipid-modifying drug	Not yet recruiting	Phase 2	December 2023
NCT05213624	BI764198	*TRPC6* inhibitor	Recruiting	Phase 2	August 2023
NCT05183646	DMX-200 (repagermanium)	*CCR2* inhibitor	Recruiting	Phase 3	June 2026
NCT05314231	ALXN1720	Anti-C5 mini-body	Not yet recruiting	Phase 1	March 2023
NCT05237388	Baricitinib	Janus kinase-*STAT* inhibitor	Not yet recruiting	Phase 2	March 2026
NCT00814255	Adalimumab	Antihuman TNF-α antibody	Completed	Phase 2	February 2014
NCT04009668			+TR-MCD: Recruiting	Phase 2	July 2024
NCT05441826	VB119	Anti-CD19 antibody	Recruiting	Phase 2	February 2024
NCT04983888	Obinutuzumab	Anti-CD20 antibody	Recruiting	Phase 2	September 2024

M de Cos et al. Kidney Int Rep (2023)

What is on the horizon? GR inhibition in nephrotic syndrome



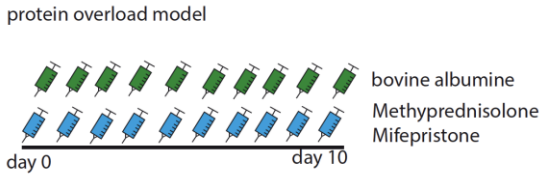
LKIV synaptopodin GR

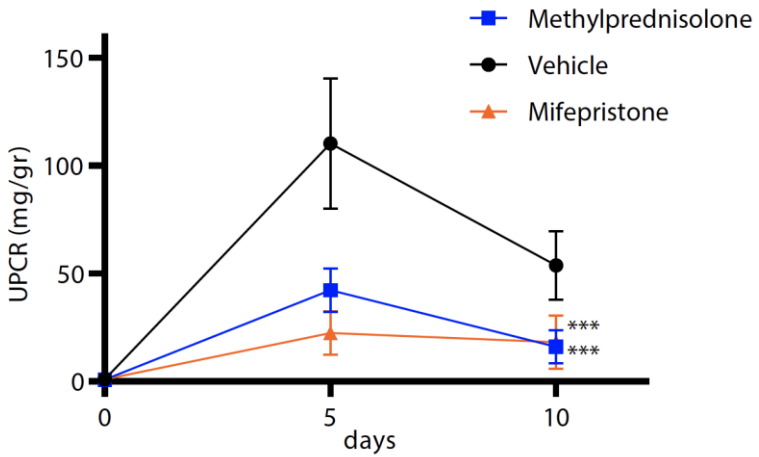


Stamellou E. et al. NDT under Revision

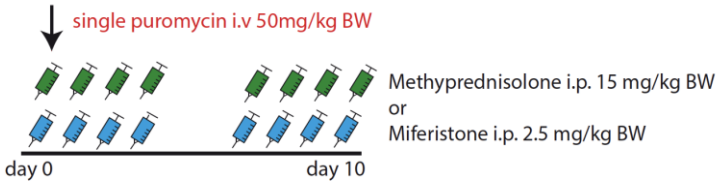
Treatment with Mifepristone

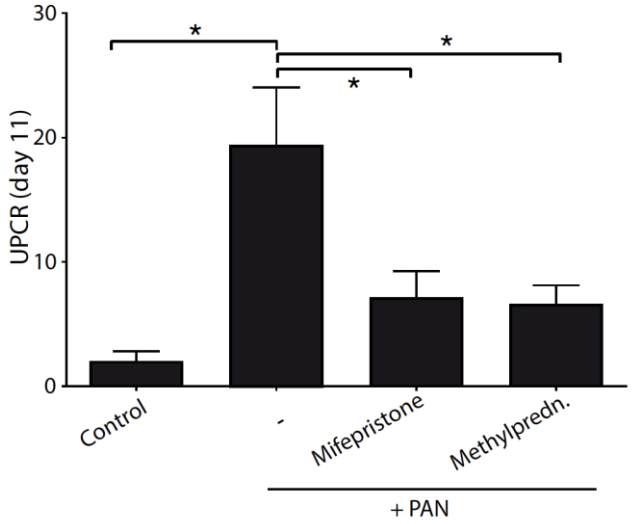
wt-mice



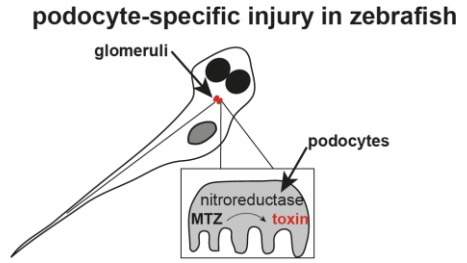


Rats

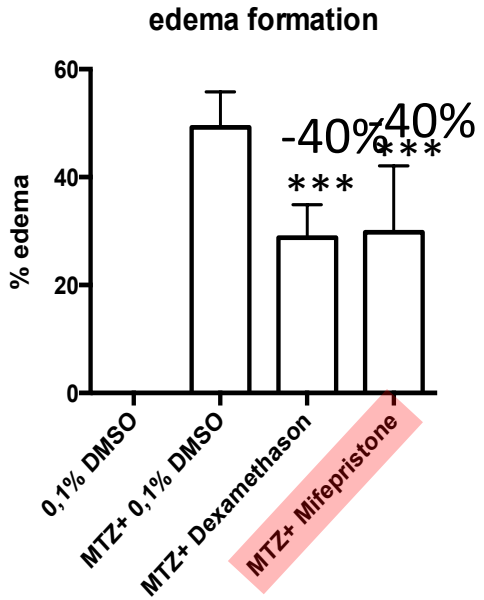




Zebrafish



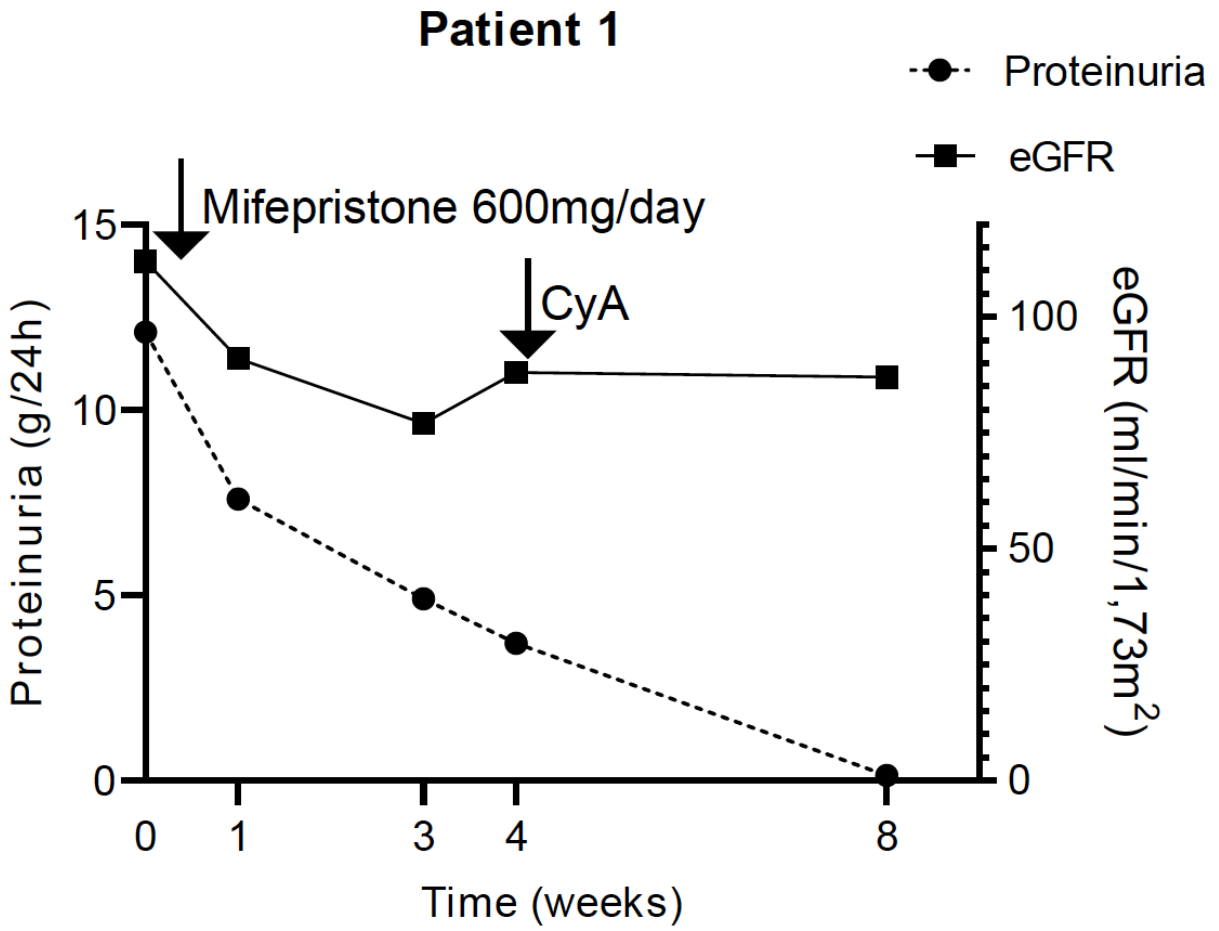
nitroreductase model



Stamellou E. et al. NDT under Revision

Individual patients treated with mifepristone

- 42-year-old man with NS , recently diagnosed with primary FSGS
- BMI 38



Stamellou E. et al. NDT under Revision

Patient #2

- A Caucasian male, 30 years old with:

✓24h urine protein 6g/day

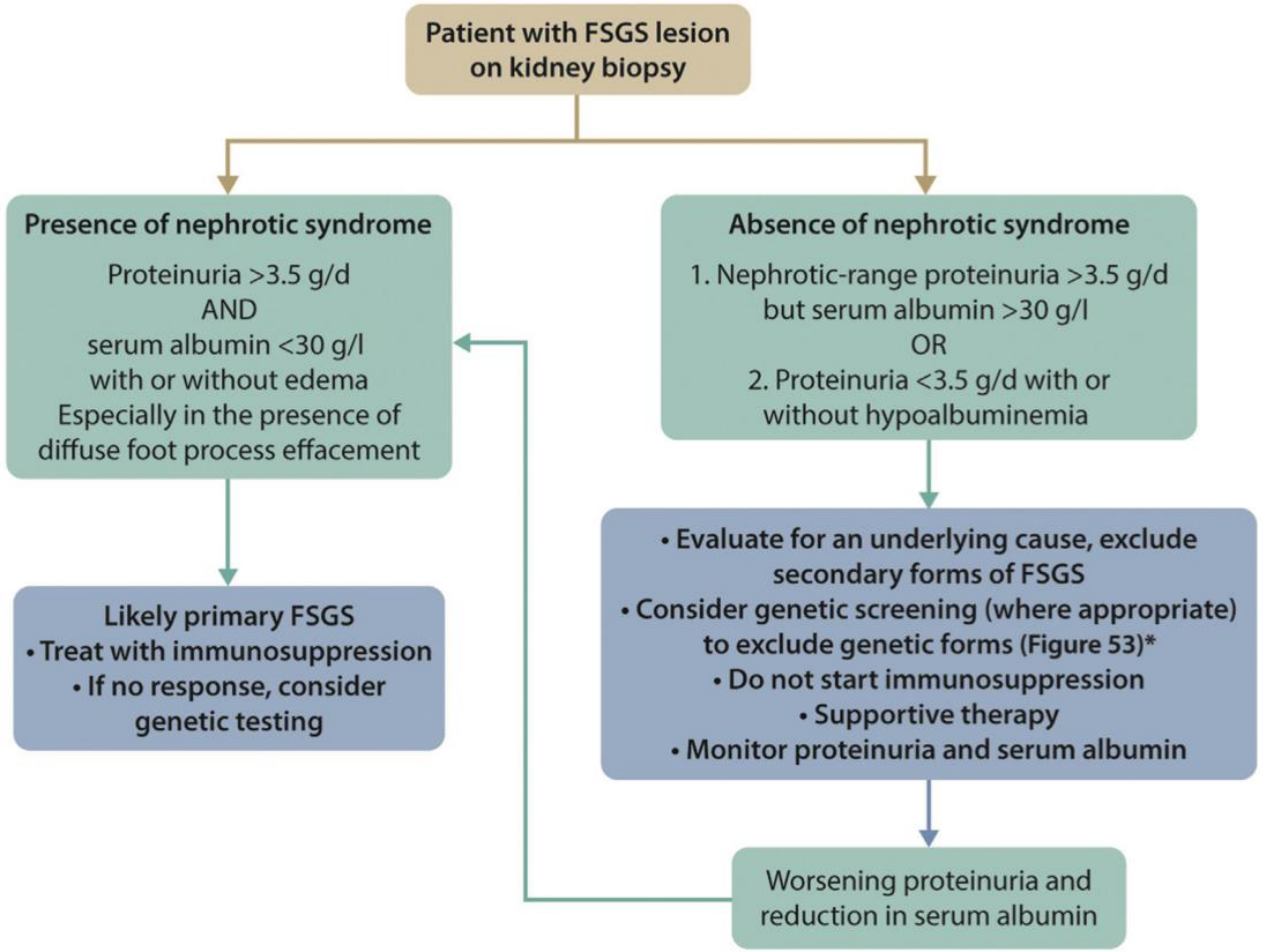
✓Normal total protein and serum albumin

✓No edema, increased BP (150/100mmHg)

- **Light microscopy: 18 glomeruli: 2 global sclerotic and 5 with FSGS**
- **Electron Microscopy:** partial FPE

→Primary FSGS with 40% tubulointerstitial fibrosis

Approach to treatment with secondary FSGS



Patient #2

- A Caucasian male, 30 years old with:

✓24h urine protein 6g/day

✓Normal total protein and serum albumin

✓No edema, increased BP (150/100mmHg)

Extended medical history:

➢ Low Birth weight 2400 gr, 48 cm

➢ Salt consumption 18 gr/day

➢ High energy protein drinks

- **Light microscopy: 18 glomeruli: 2 global sclerotic and 5 with FSGS**
- **Electron Microscopy:** partial FPE

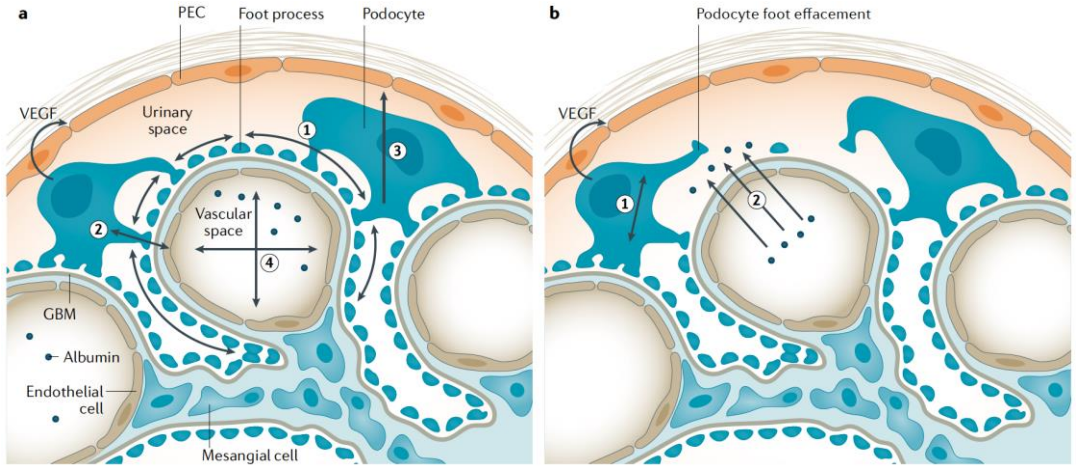
→Primary FSGS with 40% tubulointerstitial fibrosis

Approach to secondary/maladaptive FSGS

Correct the haemodynamic abnormalities →podocyte shear stress → podocyte injury

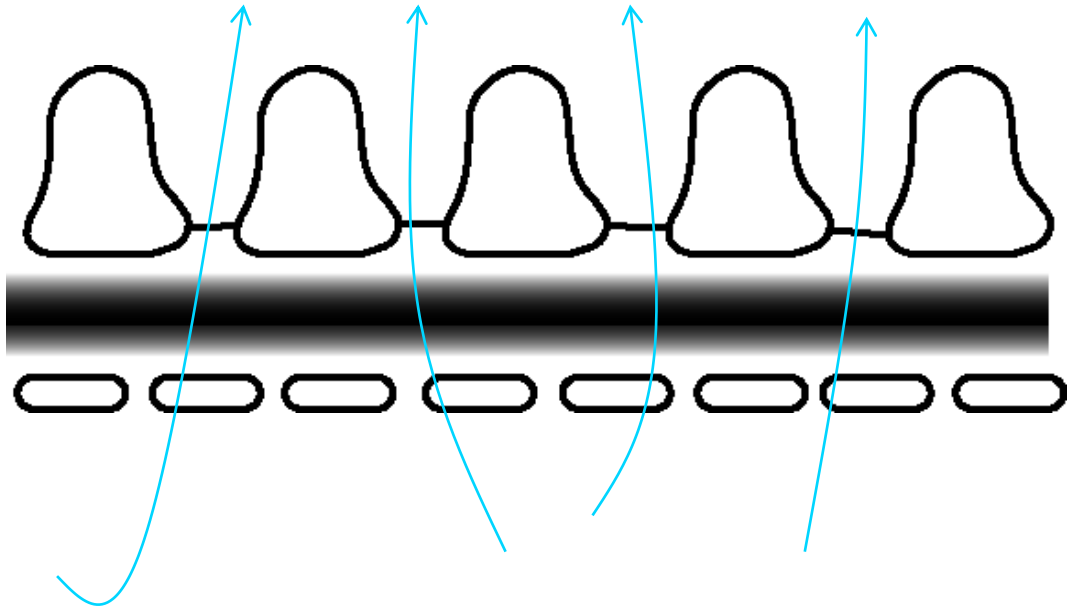
NO IMMUNOSUPPRESSION

- Dietary sodium restriction
- Protein restriction
- BP control
- RAASi
- SGLT2i



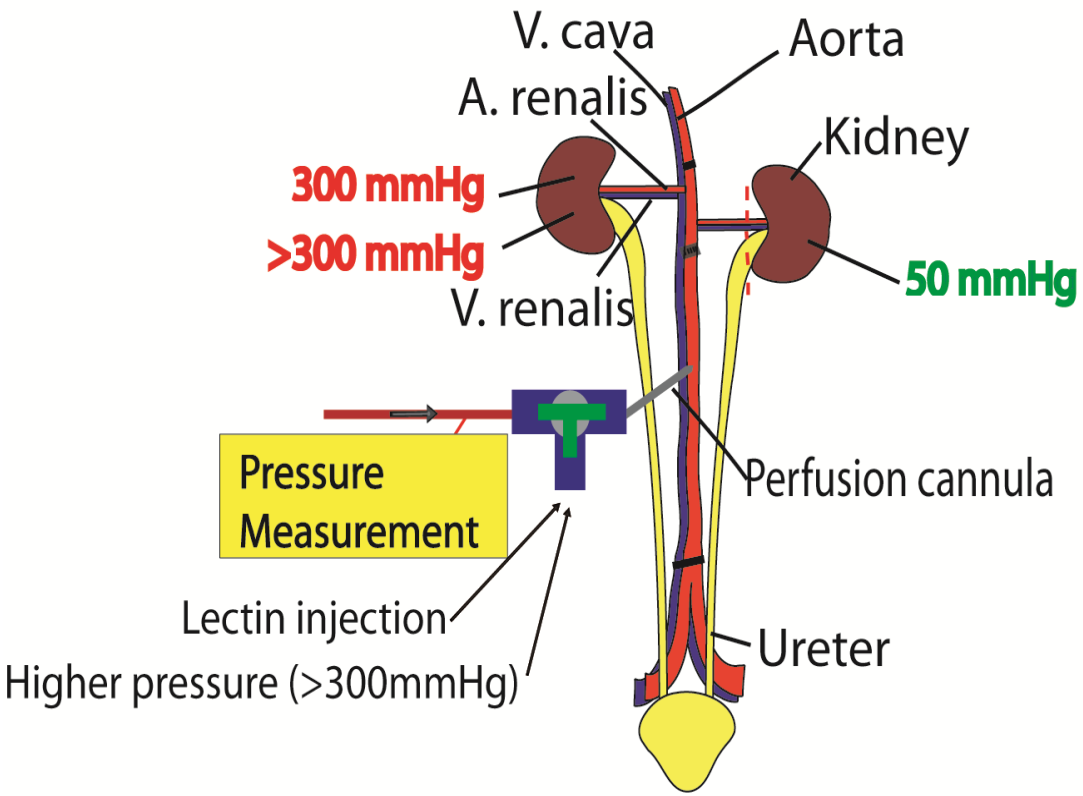
De Vriese AS Nat Rev Nephrol. 2021 Sep

Is it possible to blow podocytes off the GBM?

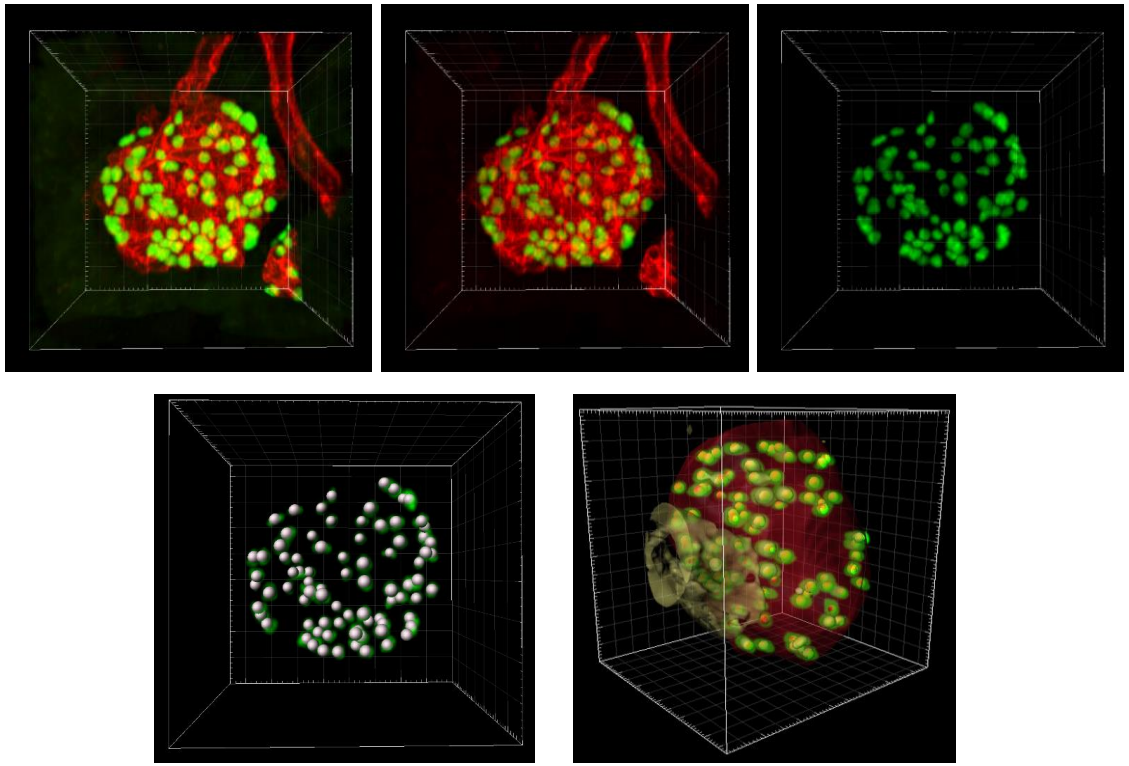


Strieder... Stamellou. Cell Physiol Biochem, 2020

Ex-vivo hyperperfusion of the right mouse kidney

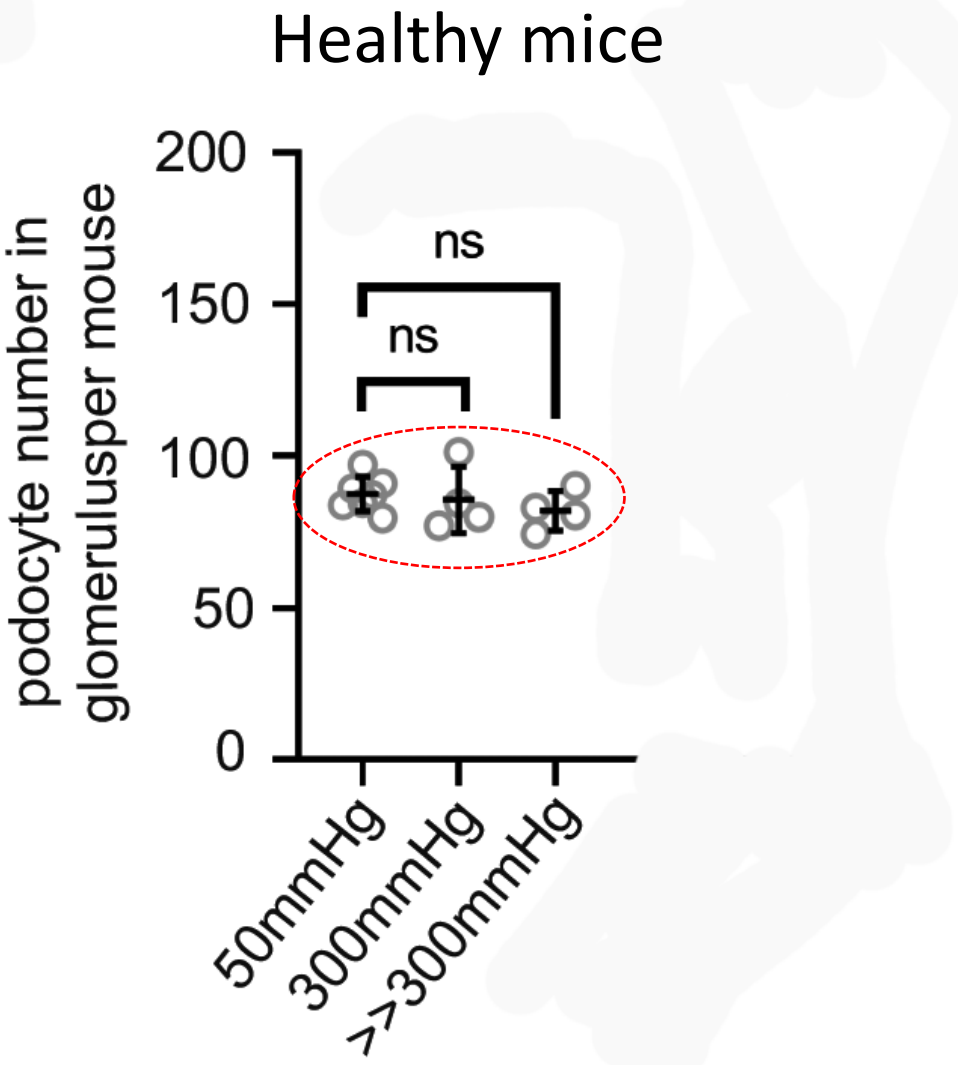


Semi-automating counting



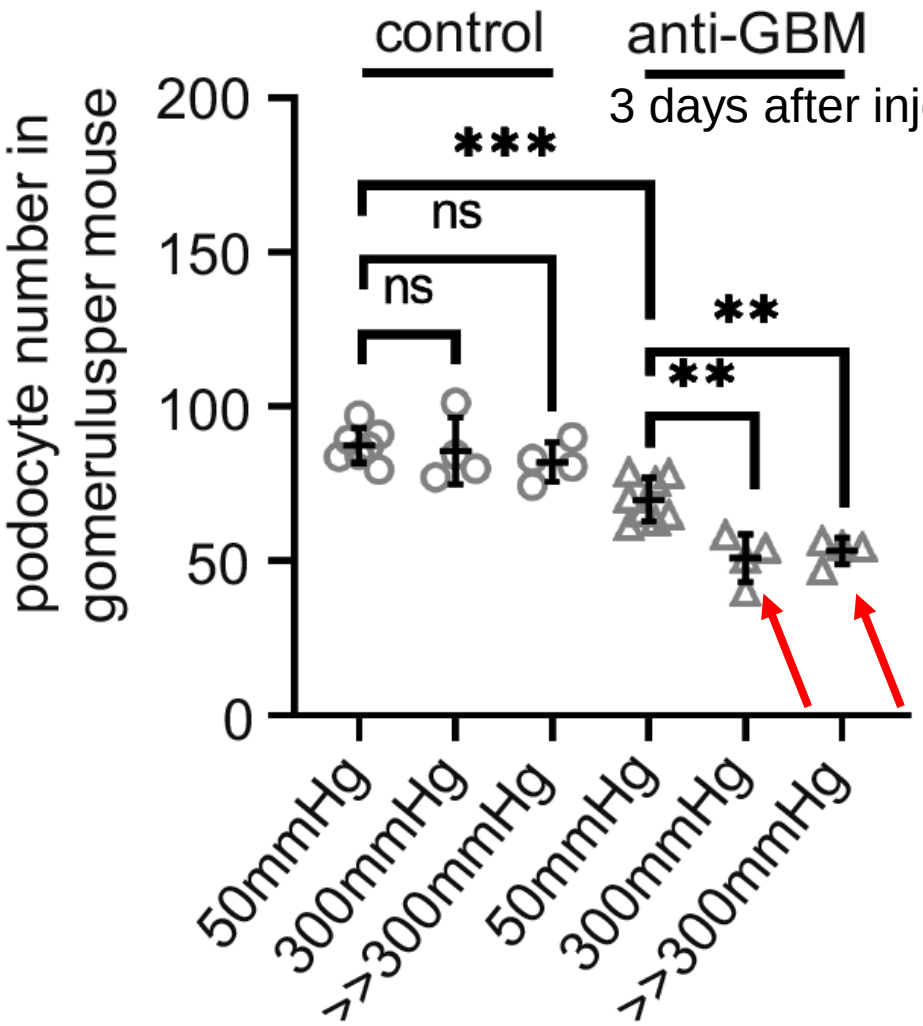
Strieder... Stamellou, Cell Physiol Biochem, 2020

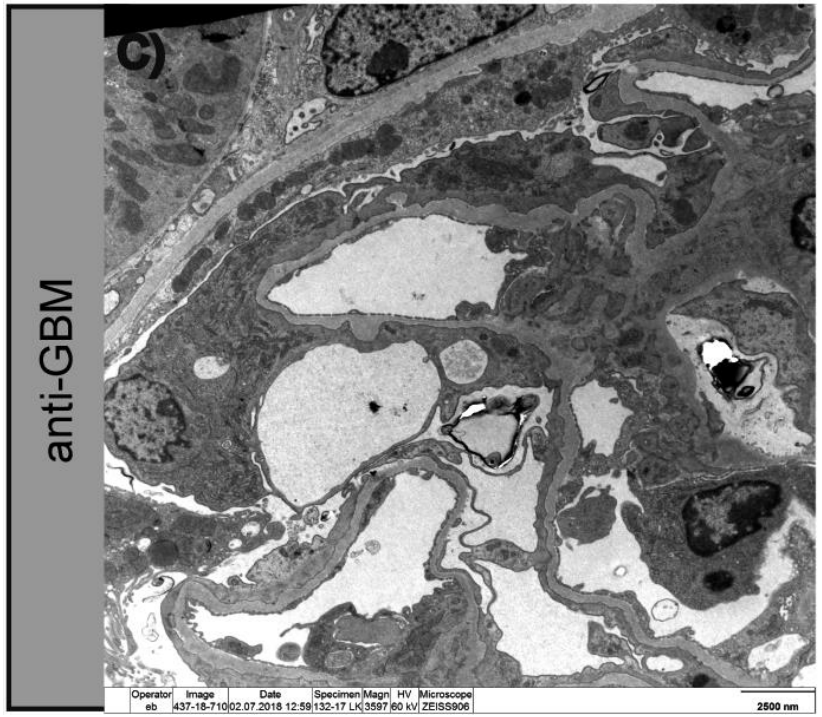
It is impossible to blow off podocytes in healthy mice

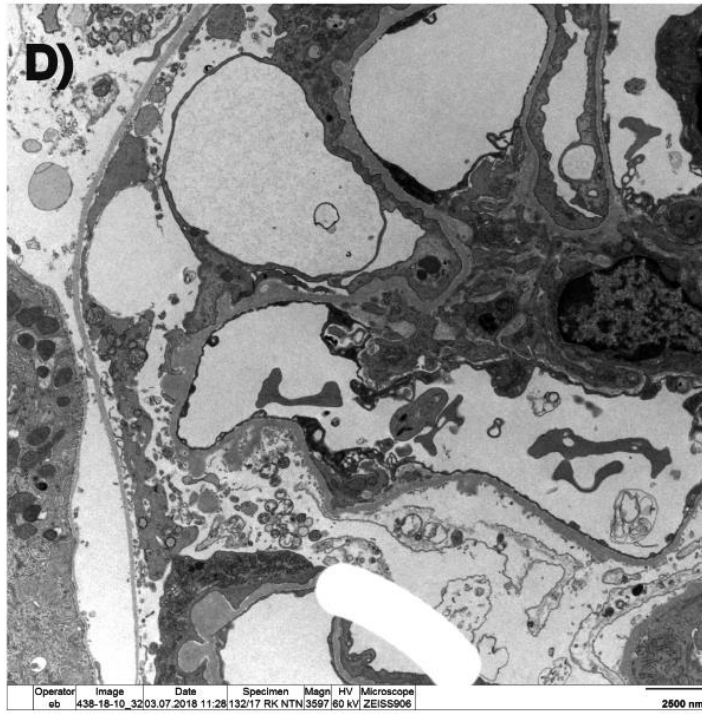


Strieder... Stamellou, Cell Physiol Biochem, 2020

Foot process effacement renders podocytes more susceptible to detachment.



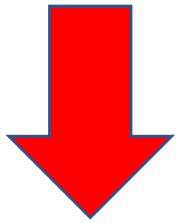




Strieder... Stamellou, Cell Physiol Biochem, 2020

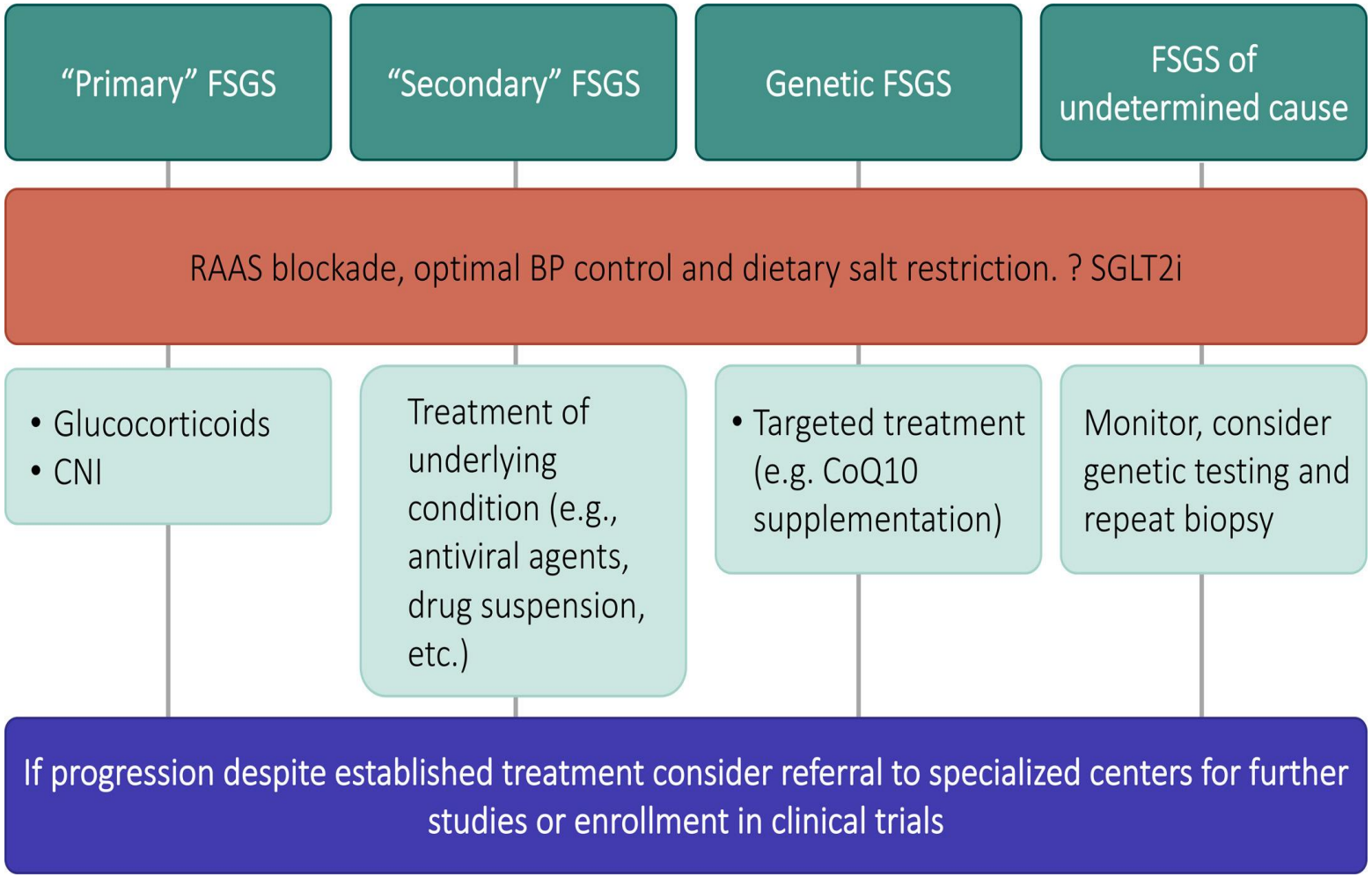
Translational message

✓Acute podocyte injury with effacement, renders podocytes susceptible to detachment at increased perfusion pressures.



Supportive therapy in glomerular diseases

Treatment approach for FSGS



Kidney International Reports 2023 830-35DOI: (10.1016/j.ekir.2022.10.004)

Goal of therapy in maladaptive FSGS

For patients with maladaptive and genetic forms of FSGS, a 30–40% reduction in proteinuria and preservation of eGFR seem appropriate surrogate markers and therapeutic targets.

→ Based on data from meta-analysis studies in patients with CKD

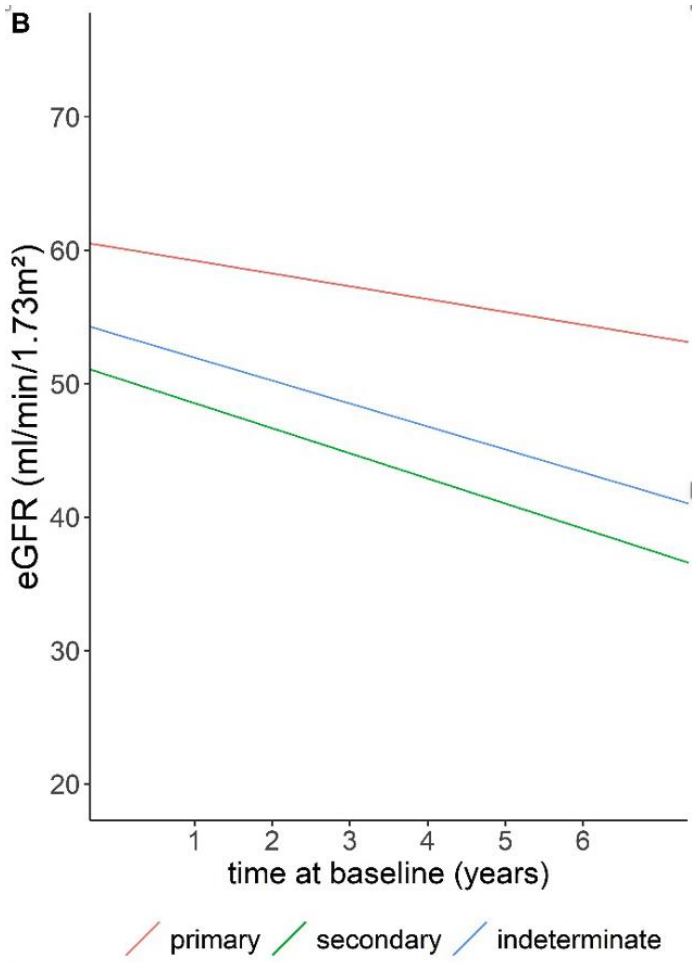
Heerspink, H. J. L. et al. *Lancet Diabetes Endocrinol.* **7**, 128–139 (2019)
Coresh, J. et al. *Diabetes Endocrinol.* **7**, 115–127 (2019)

The natural history of FSGS in the German Chronic Kidney Disease (GCKD) cohort

159 patients with biopsy-proven FSGS

Table 3. Multivariate cox model

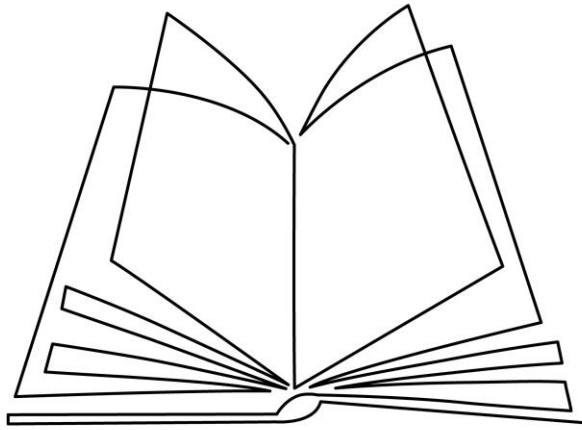
		MAKE N =44/159 HR [95% CI]	MACE N=16/159 HR [95% CI]
age per 10 years (BSL)		0.81[0.63;1.04]	1.47[0.84;2.58]
sex	female	0.98[0.5;1.91]	0.21[0.04;1]
	male	reference	reference
BMI per 5 (BSL)		1.12[0.81;1.55]	2.43[1.34;4.39]
UA/C-C for FSGS	>= 0.7 g/g	5.27[2.4;11.55]	3.37[1.05;10.82]
	< 0.7 g/g	reference	reference
eGFR per 10		0.79[0.66;0.93]	0.63[0.46;0.88]
FSGS etiology	indeterminate	1.44[0.63;3.28]	
	secondary	0.74[0.35;1.57]	0.64[0.19;2.08]
	primary	reference	reference



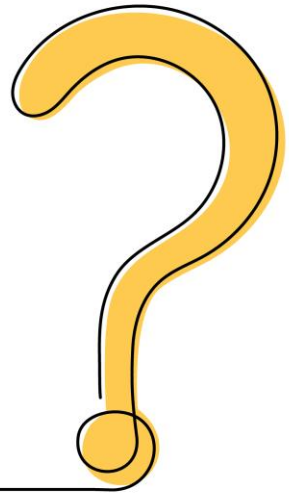
Stamellou E et al. unpublished data

Conclusions

- The identification of an FSGS lesion in a kidney biopsy of a patient with proteinuria does not establish a specific diagnosis
- A correct differential diagnosis between ppfFSGS, secondary and genetic FSGS in adults requires a clinicopathological approach.
- Supportive treatment is the cornerstone in the treatment of all FSGS forms



Thank you !!



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