

Renal update

Jasmine Tan

Mr TP

Poor diabetic control and progressive proteinuria

- Poor medication adherence, no meds for 3-4 years while overseas
- Needle phobia
- Previous NSAID exposure post fall
- No arthritis or new rash
- No back pain
- No recent infection
- Noticed 10 kg weight gain over 4 months

35 yo male

1. Type 2 diabetes (2013, age 26)

- GAD and IA2 antibodies negative
- Commenced on insulin 2014
- HbA1c >100 since 2013
- Proliferative diabetic retinopathy with retinal haemorrhage (2021), treated with Avastin

2. CKD G3a A3 with nephrotic range proteinuria

- Albuminuria since 2013
- Progression to nephrotic range proteinuria documented 2022
- Serum albumin 23 g/L
- Bland urine microscopy
- Previous AKI with gastroenteritis

3. Hypertension
4. Previous balanitis
5. Hyperlipidaemia
6. Fatty liver disease
7. Increased BMI
8. Non smoker

Medications

Lantus 30 units mane

Metformin 500 mg twice daily

Empagliflozin 10 mg daily

Amlodipine 5 mg daily

Atorvastatin 20 mg daily

On examination

BSLs 17 – 20 mmol/L at home

Weight 94kg

Seated automated BP 183/112 mmHg (1), 177/110 mmHg (2)

Heart rate 83 bpm and regular

Heart sounds dual, no parasternal heave

Chest clear

Significant sacral and pedal oedema



Investigations

HbA1c 86 mmol/mol (improved from 100s)

Creatinine **177** $\mu\text{mol/L}$; eGFR **42** ml/min; urine ACR **1129.3** mg/mmol

Urine microscopy $<10 \times 10^6/\text{L}$ leukocytes, $<10 \times 10^6/\text{L}$ rbc, epi $4 \times 10^6/\text{L}$

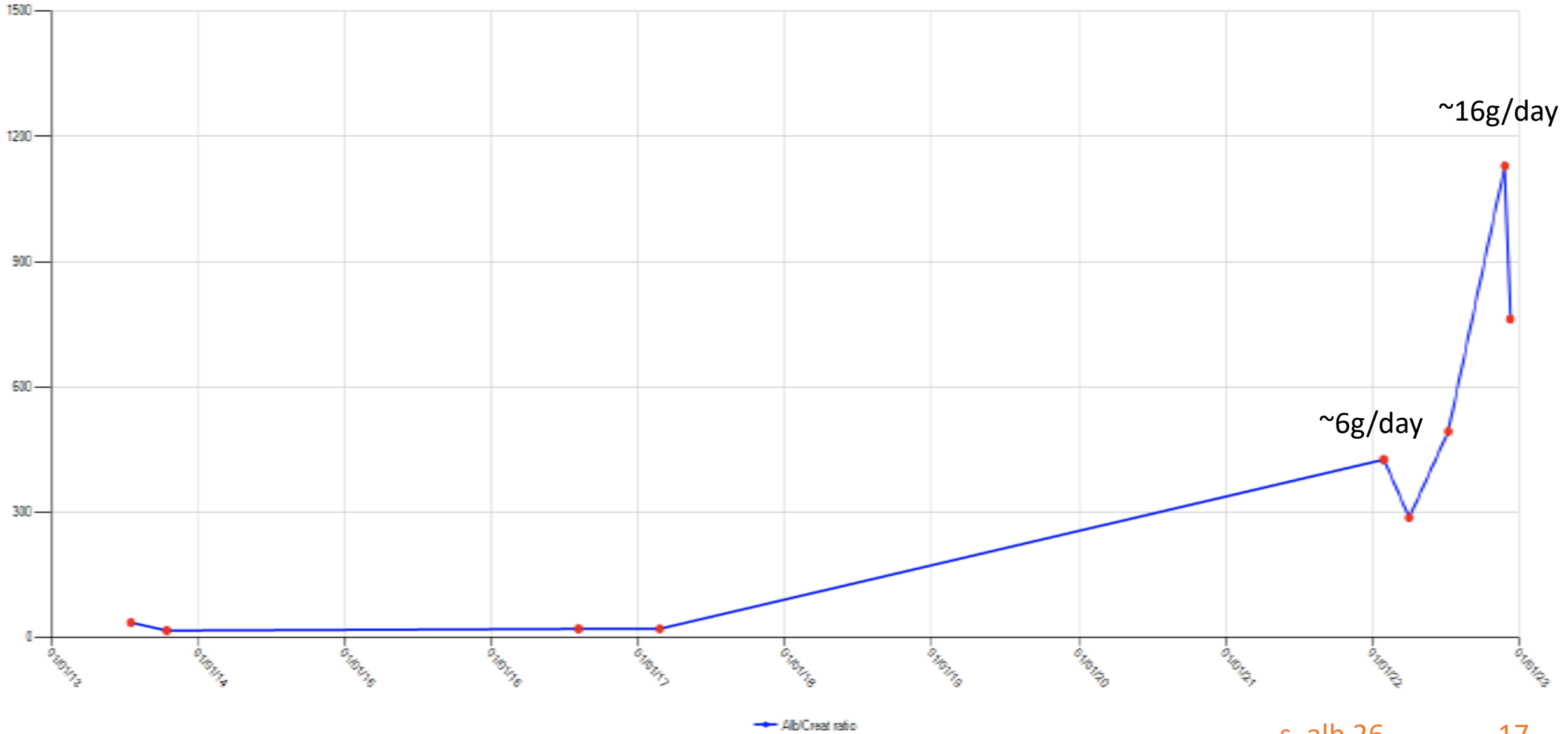
Serum albumin **17** mmol/L

Cholesterol **10.4** mmol/L; TG **3.5** mmol/L; HDL 1.34 mmol/L; LDL **7.2** mmol/L; ratio 7.8

KUB ultrasound: Bilateral kidneys normal in size. Increased echogenicity in right renal upper pole, likely containing cysts.

No obstruction or nephrocalcinosis

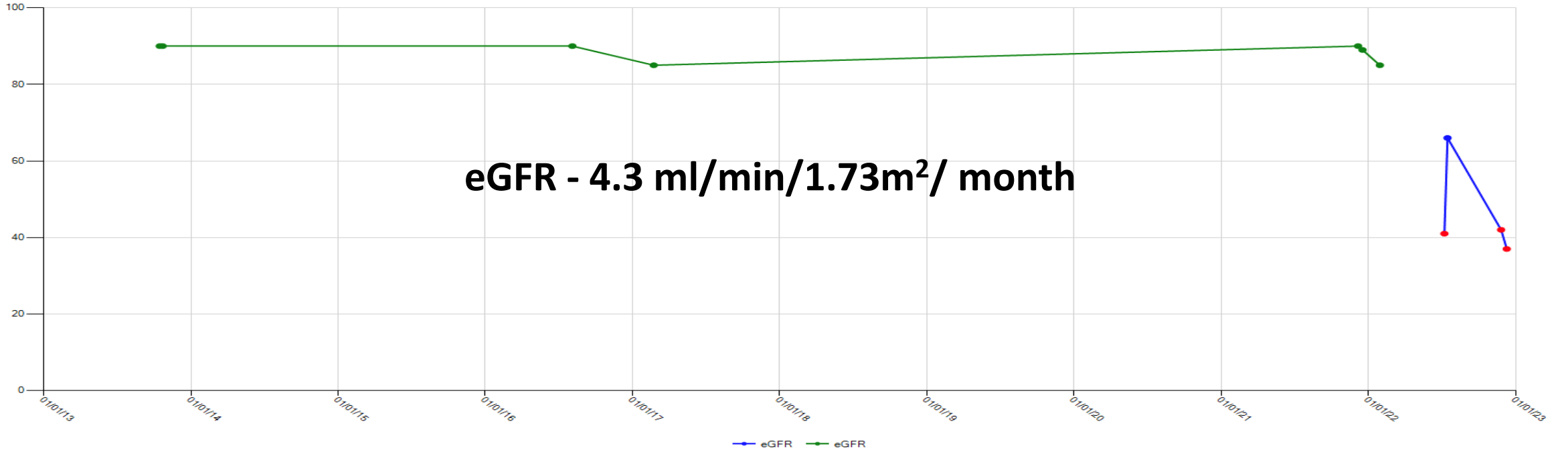
ALBUMIN CREATININE RATIO 18/07/13 10:10 - 10/12/22 08:05



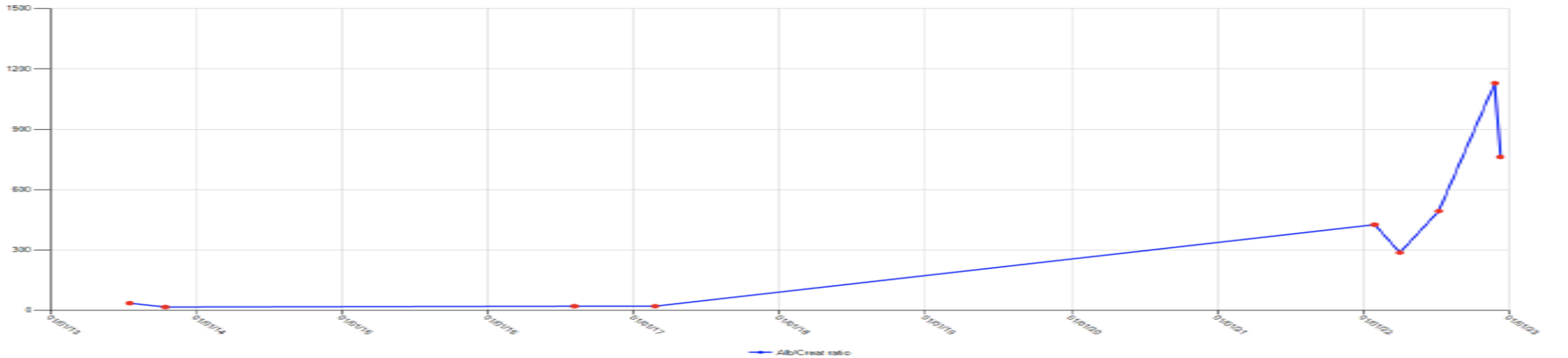
s. alb 26

17

RENAL FUNCTION TESTS 15/10/13 11:41 - 10/12/22 08:05



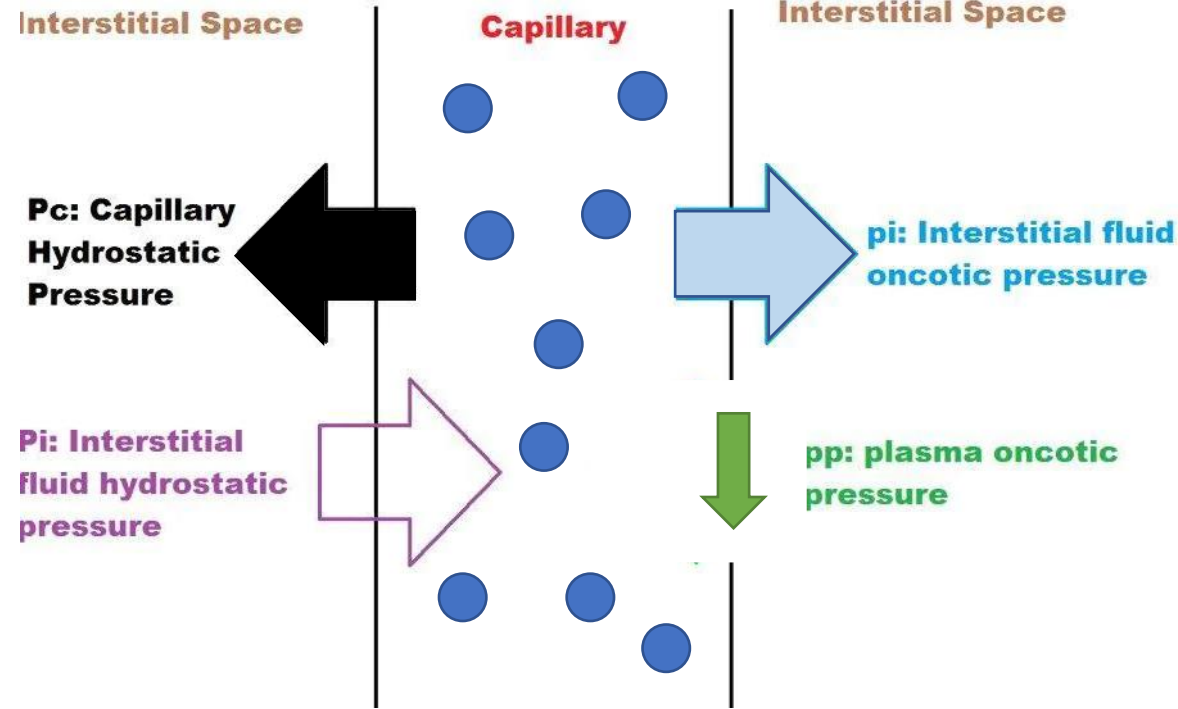
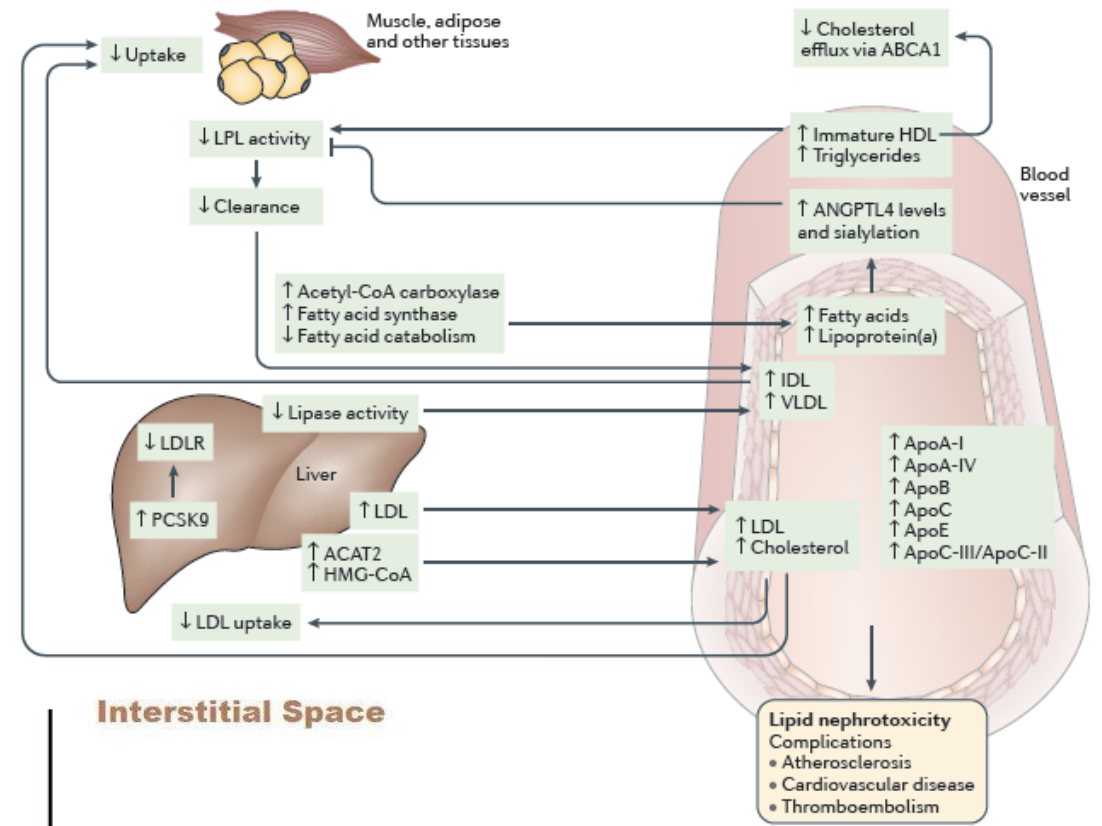
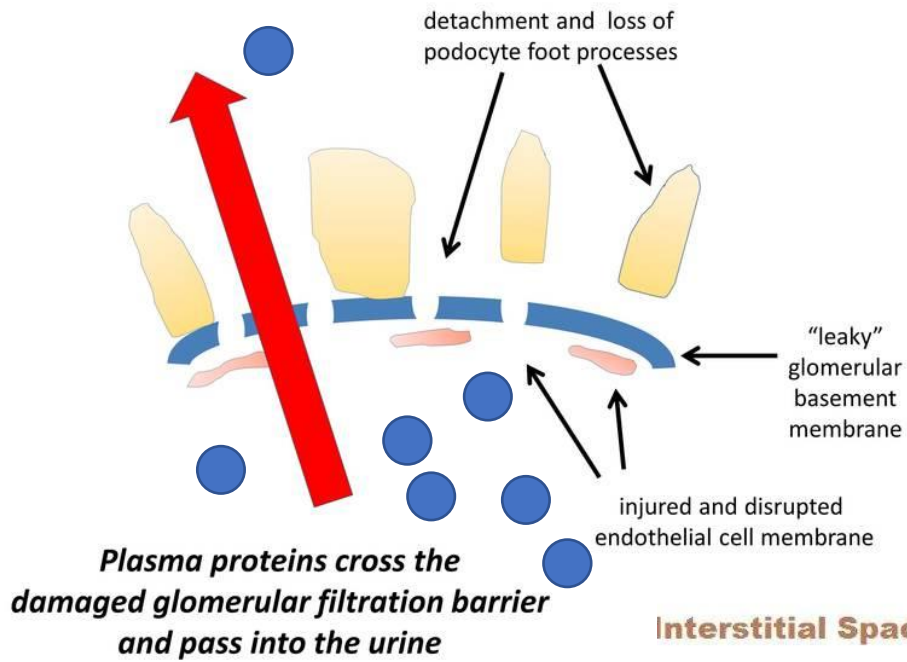
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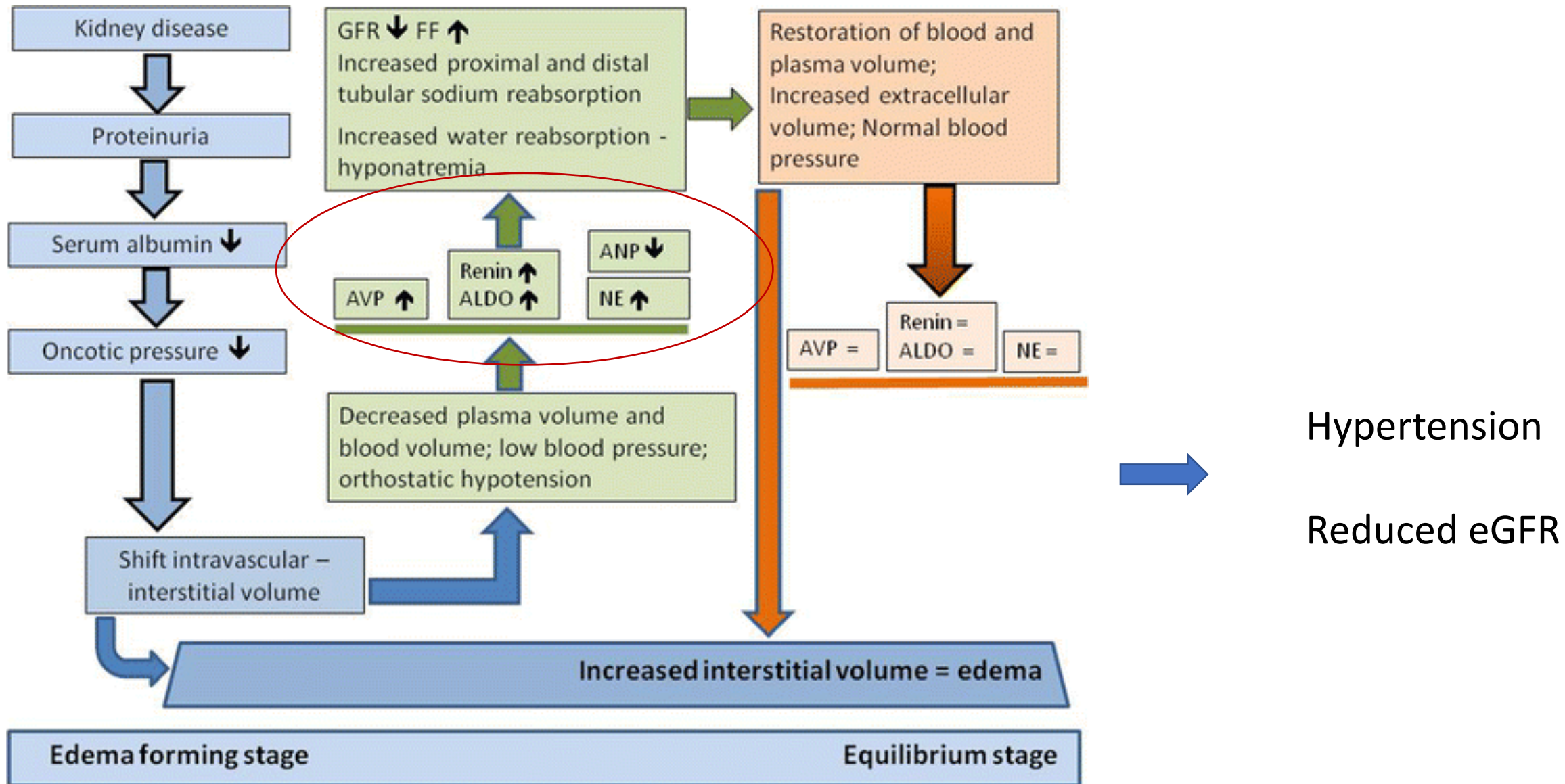
Nephrotic syndrome

- Heavy proteinuria (>3.5 g/ 24 hours)
- Hypoalbuminemia (< 30 g/L)
- Peripheral oedema
- Hyperlipidemia

- Hypertension
- Acute renal impairment
- Increased risk of thrombotic disease



Nature Rev Nephrology 2018; 14, 57–70.



What is the potential cause for nephrotic syndrome?

- A. Advanced diabetic nephropathy
- B. Focal segmental glomerulosclerosis (FSGS)
- C. Membranous nephropathy
- D. Amyloidosis
- E. Systemic lupus erythematosus

Further investigations

- Serum free light chains - kappa **74** mg/L (3 – 19); lambda **56** mg/L (6 – 26); ratio 1.31 (0.26 – 1.65)
- Normal serum electrophoresis, serum calcium 2.22 mmol/L
- PLA2 IgG <2 (<14 negative)
- ENA negative
- Complements C3 and C4 normal
- Hep B and Hep C serologies negative
- HIV negative
- Urate 0.52 mmol/L (0.23 – 0.42)

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Presentation, pathology and prognosis of renal disease in type 2 diabetes

Jasmine Tan,^{1,2} L Jonathan Zwi,³ John F Collins,⁴ Mark R Marshall,⁵ Tim Cundy^{1,6}

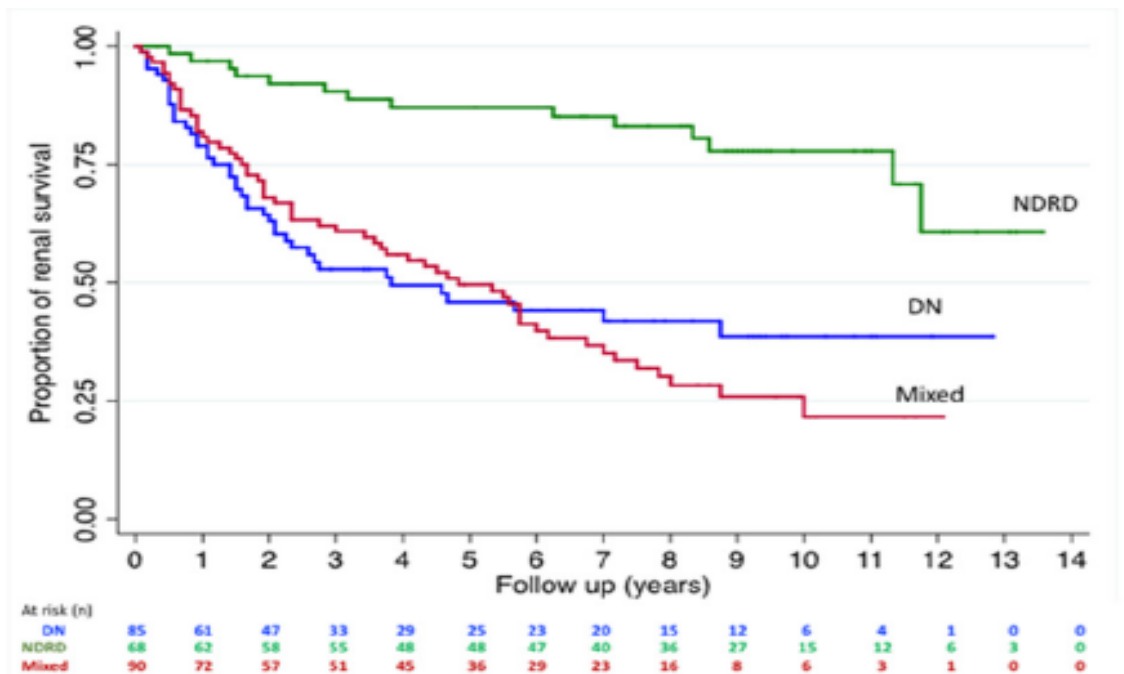
263 patients with type 2 diabetes with renal biopsies (2002 – 2008)

- AKI
- Progressive CKD or proteinuria without other microvascular complications

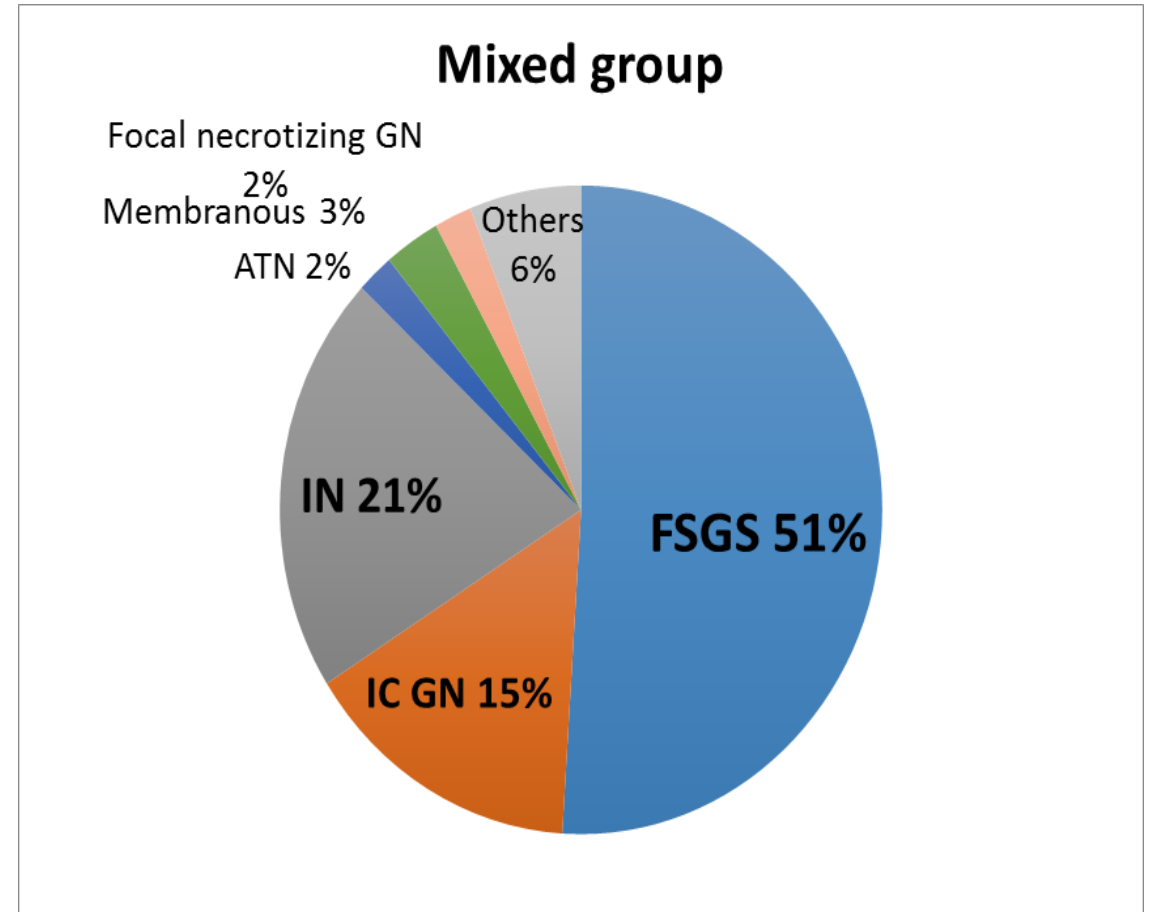
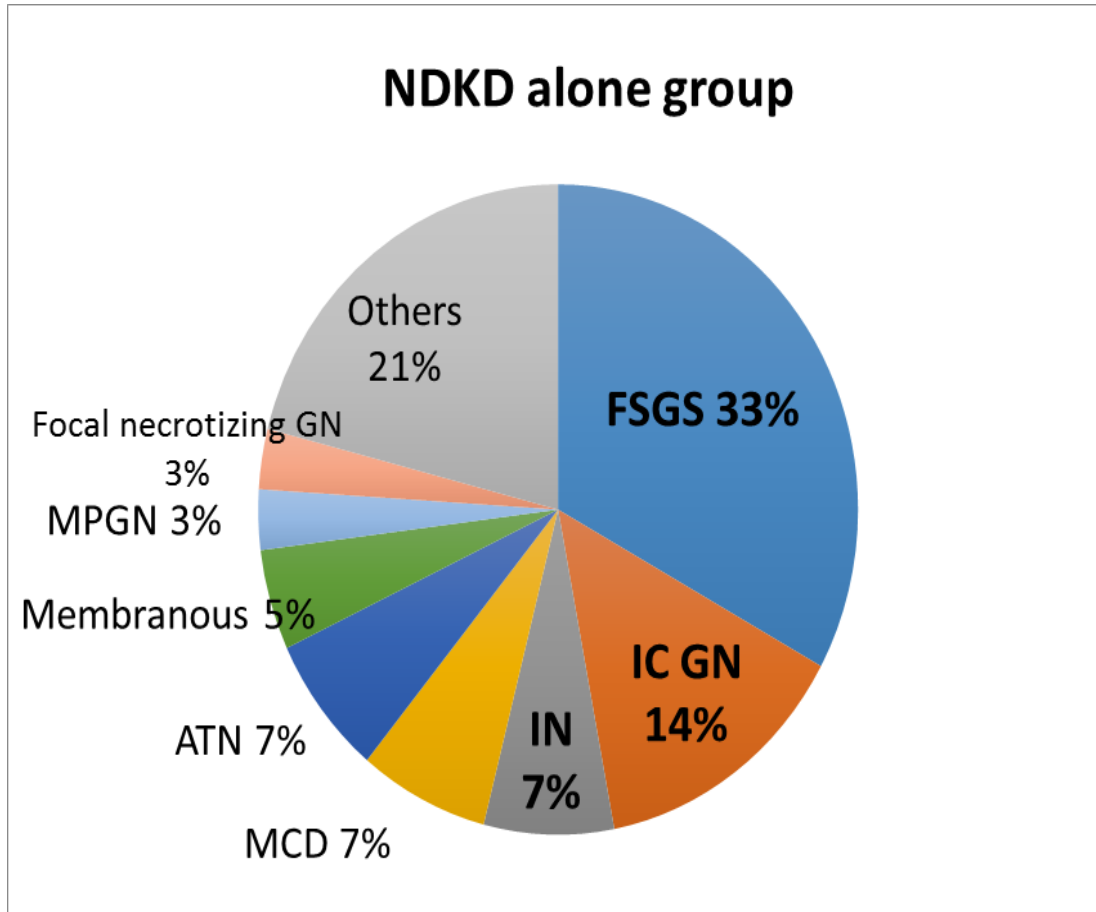
3 groups:

- Diabetic nephropathy (DN) **36%**
- Non diabetic renal disease (NDRD) **37%**
- Mixed (DN + NDRD) **27%**

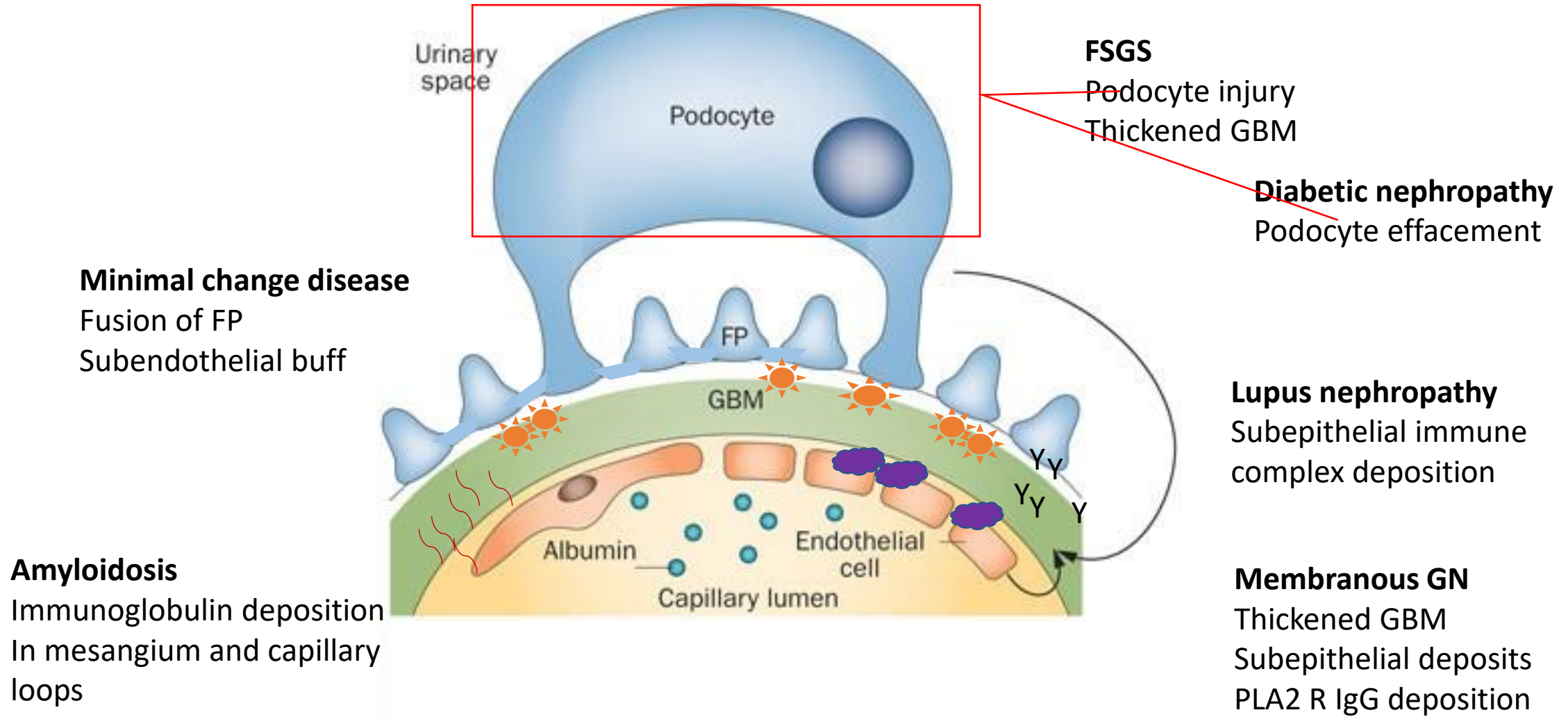
- Poorer renal prognosis compared to the NDRD group following adjustment
- Corresponded with advanced renal lesions and AKI



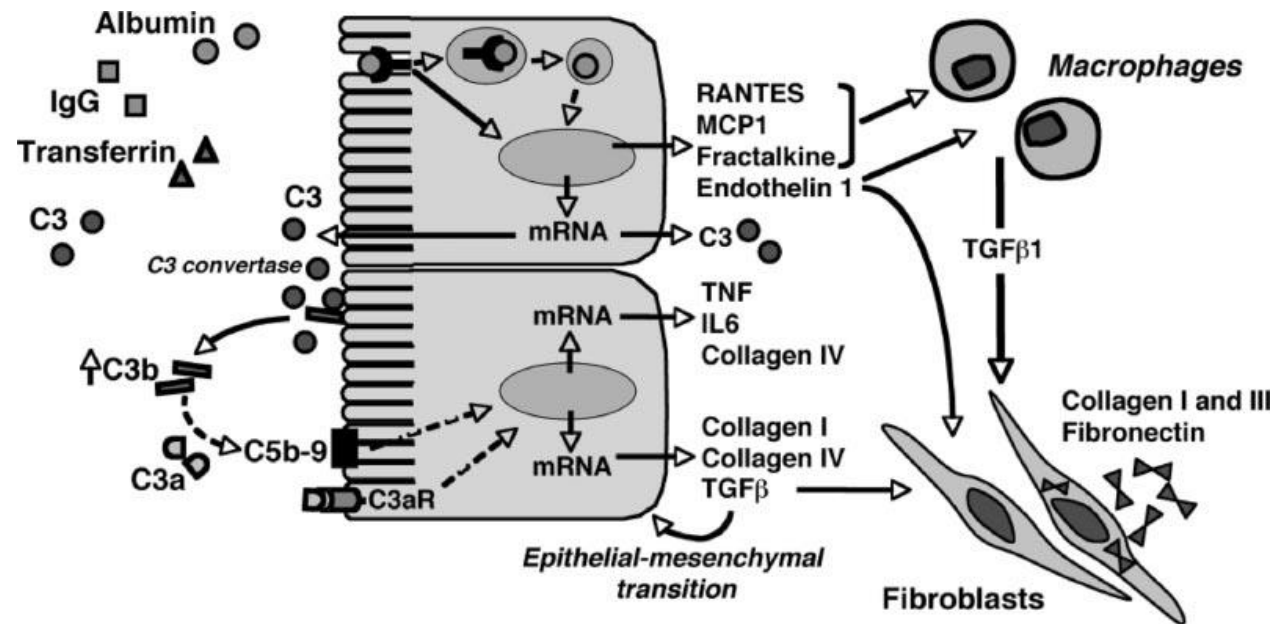
High prevalence of non-diabetic renal disease in T2D



Glomerulopathies



Proteinuria nephrotoxicity



- Proteinuria – pathogenetic role in progression to ESRD and CV risk
- Activation of inflammatory and fibrogenic pathways in proximal tubules

- Albuminuria strong predictor for CKD development
- Normoalbuminuria in 24% (T1D); 36 – 50% (T2D)

**Prognosis of CKD by GFR
and Albuminuria Categories:
KDIGO 2012**

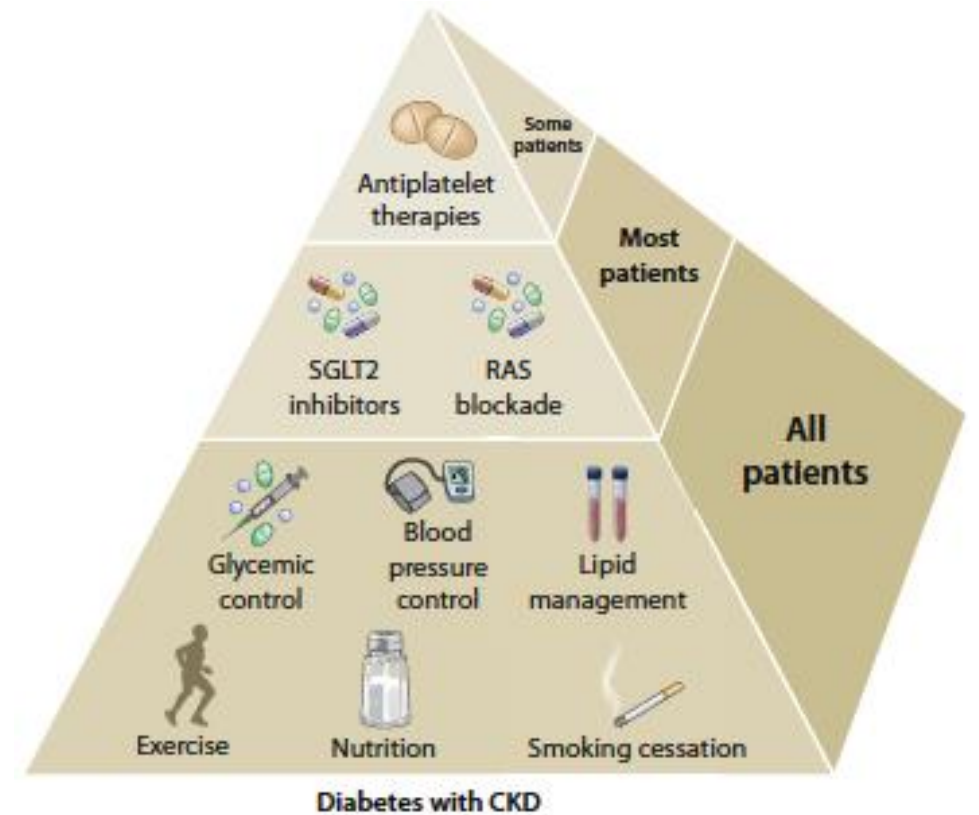
			Persistent albuminuria categories Description and range			
			A1	A2	A3	
			Normal to mildly increased	Moderately increased	Severely increased	
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (mL/min/ 1.73 m²) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-89	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Refer to Renal Services

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

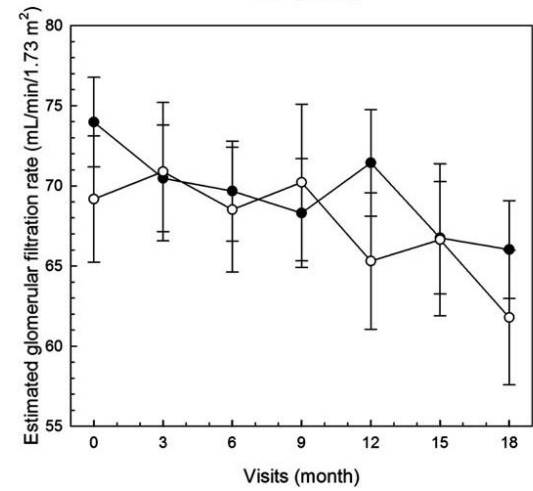
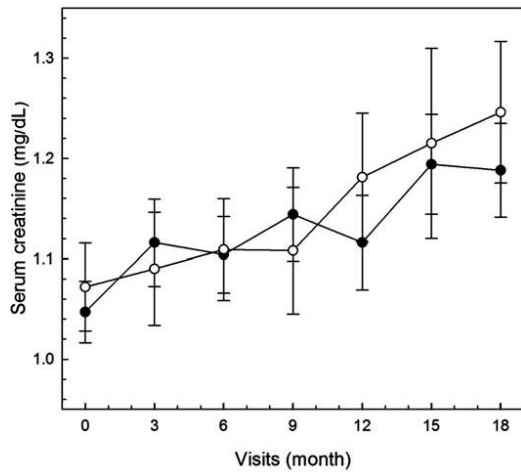
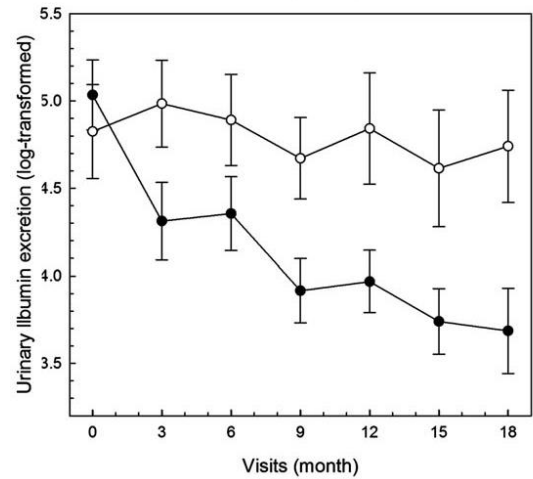
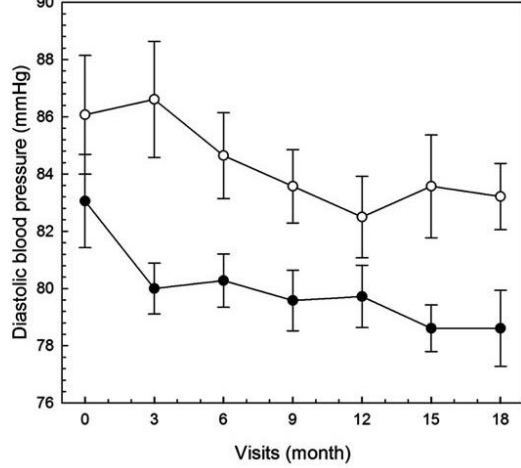
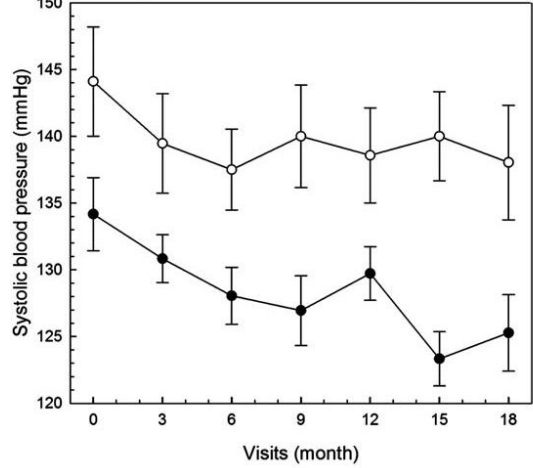
Specific therapies in DKD

- SGLT 2 inhibitors – Empagliflozin
- RAS blockers
- Mineralocorticoid receptor blockers
- Good glycaemic control
 - *RR 67% in doubling of plasma creatinine (UKPDS)*



Role of MRA in diabetic kidney disease

- Spironolactone (non-selective) and Eplerenone (selective)
- Finerenone (non-steroidal, selective)
- Role in downregulating proinflammatory and fibrogenic effects



● SPR/ARB
○ ACE inhibitor/ARB

- 18 months: SPR + ARB vs ACEi + ARB

- At 18 months

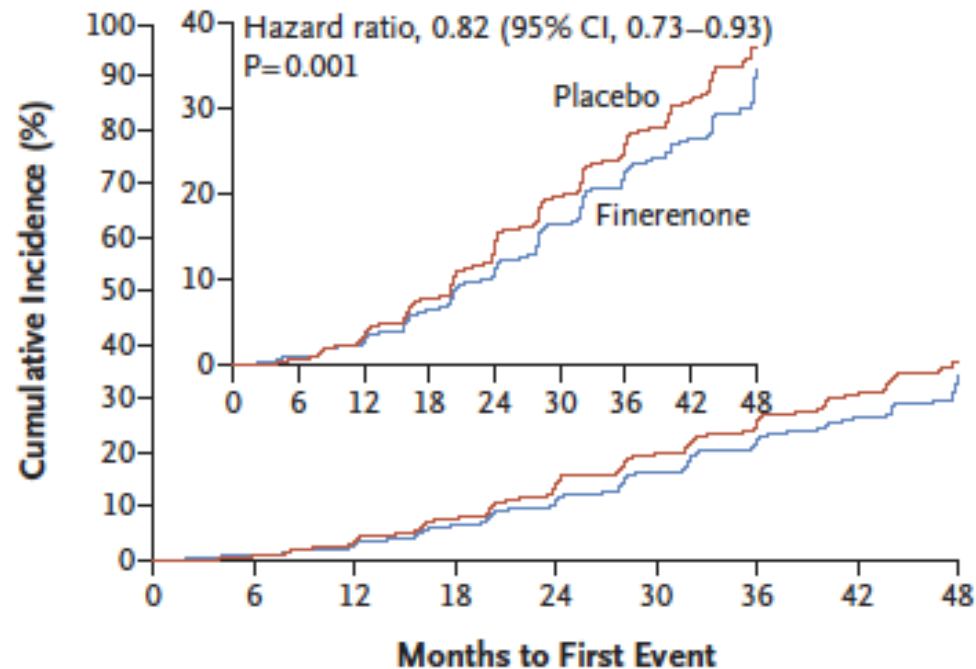
- -8.9/-4.4 mmHg vs. -6.1/-2.2 mmHg
- -60.4 mg/24 hr vs. + 22.0 mg/24 hr
- eGFR – 10.2 ml/min vs. -9.1 ml/min

- Similar effects with eplerenone

- SE hyperkalaemia & gynaecomastia
- Inferred CV and renal protective benefits

FIDELIO-DKD: Renal outcomes with Finerenone

A Primary Composite Outcome



No. at Risk

Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83

- Moderate – severe CKD population
- 88% macroalbuminuria
- Standard therapy
- 10 % on SGLT2/GLP1RA
- RR 31% reduction in albuminuria
- 1^o outcome: Consistent across CKD subgroups
- CV death RR 14%, p=0.03
- Minimal increase in serum potassium

ESRD, sustained decrease of $\geq 40\%$ from baseline eGFR, renal death

Superiority of Finerenone

- Higher selectivity of MR
- Stronger anti-inflammatory and anti-fibrotic effects
- Effects distributed between heart and kidney compared with Spironolactone effect on kidney predominantly

Back to our Mr TP: Management of NS

- Diuretics and dietary salt restriction (2g/day ~ <1 tsp/day)
 - Loop diuretics +/- thiazide
- RAS blockade & Empagliflozin
 - Reduce glomerular hyperfiltration and proteinuria
 - Possible addition of Spironolactone/Eplerenone
- Aspirin
- Statins

Summary

- Nephrotic syndrome associated with hypertension, AKI, risk of thrombosis associated with dyslipidemia
- Urine microscopy useful to exclude glomerulonephritides
- Albuminuria increases tubulointerstitial inflammation and fibrosis
 - RAS blockers
 - Empagliflozin
 - MRA

Questions?

- Thanks for your attention!