RENAL COMPLICATIONS OF SICKLE CELL DISEASE

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WHAT WE WILL COVER

Pathophysiology of renal damage in sickle cell conditions

Types of renal disease in sickle cell disease

Screening and investigations for renal disease

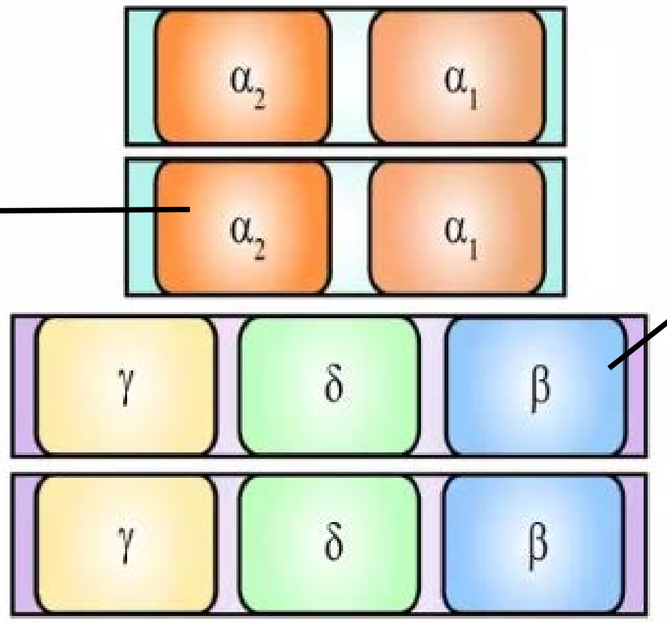
Management of renal complications

Test your knowledge

REMINDER: HAEMOGLOBINOPATHIES

Variant haemoglobins due to alpha chain mutation/deletion:

- Hb Constant Spring (--/aa(CS))
- HbH (--/-a)
- Hb Barts (--/--)



NORMAL GENES

LearnHaem

Variant haemoglobins due to beta chain mutation:

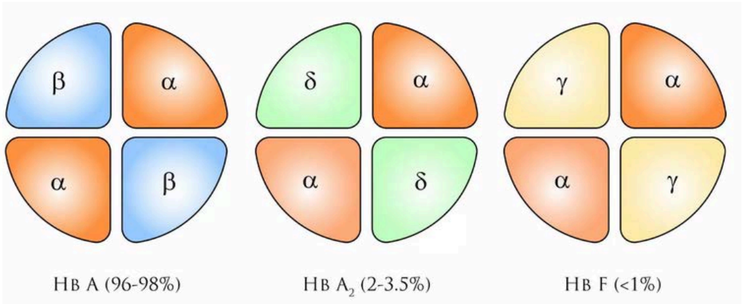
- HbS
- HbC
- HbE
- HbD Punjab

Beta chain dysfunction:

- Beta plus thalassaemia

Beta chain deletion:

- Beta zero thalassaemia



REMINDER - SICKLE CELL DISEASE

Haemoglobins are made of globin chains

Including:

- Alpha chains (present in all haemoglobins)
- Beta chains (in HbA)
- Delta chains (in HbA2)
- Gamma chains (in HbF)

Sickle cell disease is autosomal recessive

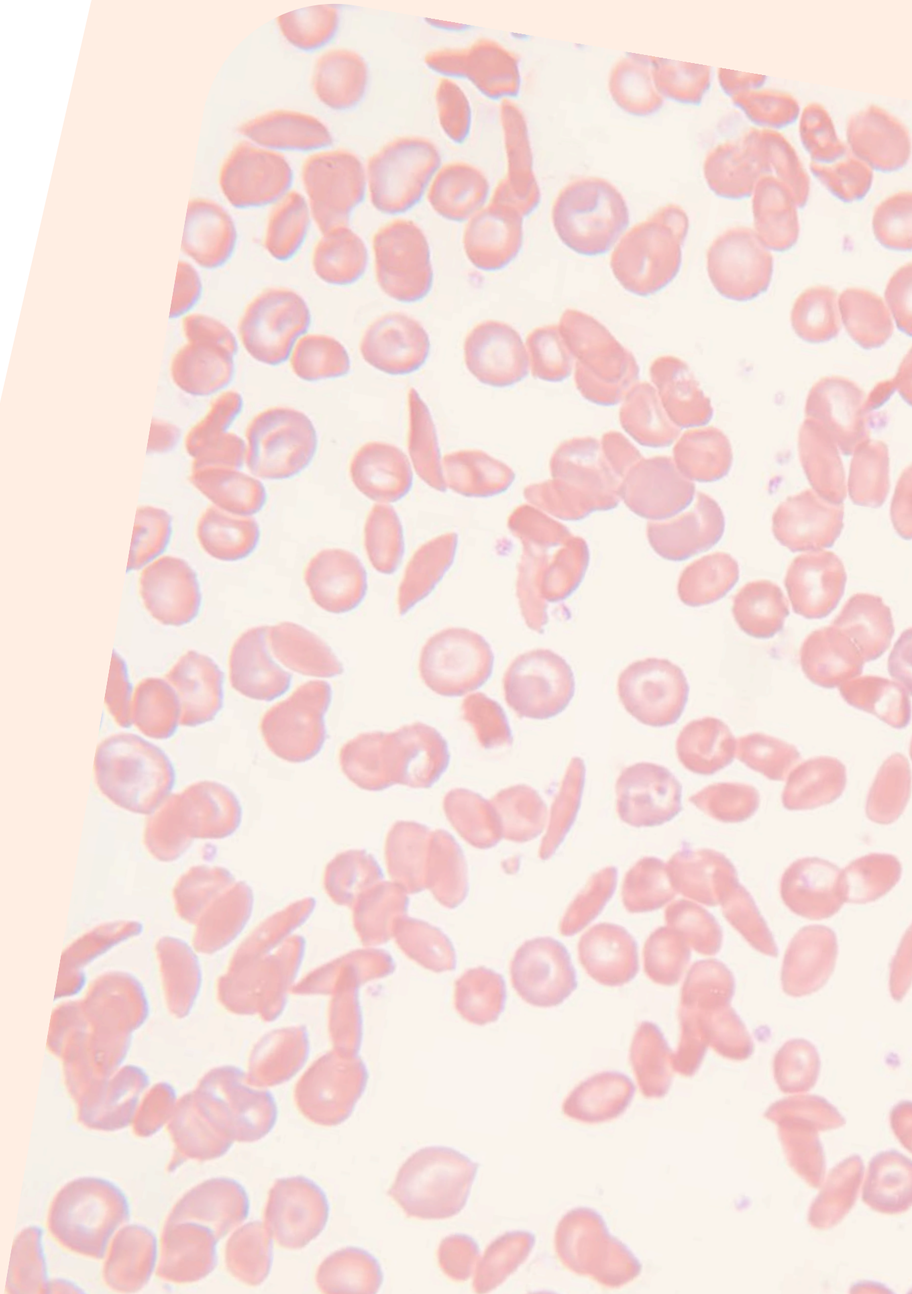
Patients with sickle cell trait have around 30% HbS, patients with sickle cell anaemia cannot make HbA.

One amino acid substitution

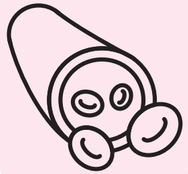
Sickle cell disease is a one amino acid substitution on chromosome 11 which creates HbS rather than the normal HbA.

Sickling of red cells

Red cells only become sickle shaped once deoxygenated, which causes HbS to polymerise. This happens irreversibly by about 10 days into the life of the red cell and it is then haemolysed.



HOW SICKLE CELLS CAUSE DAMAGE



Vaso-occlusion

Sickled cells are dehydrated and undeformable. This leads to them occluding small vessels causing ischaemia, organ damage and pain

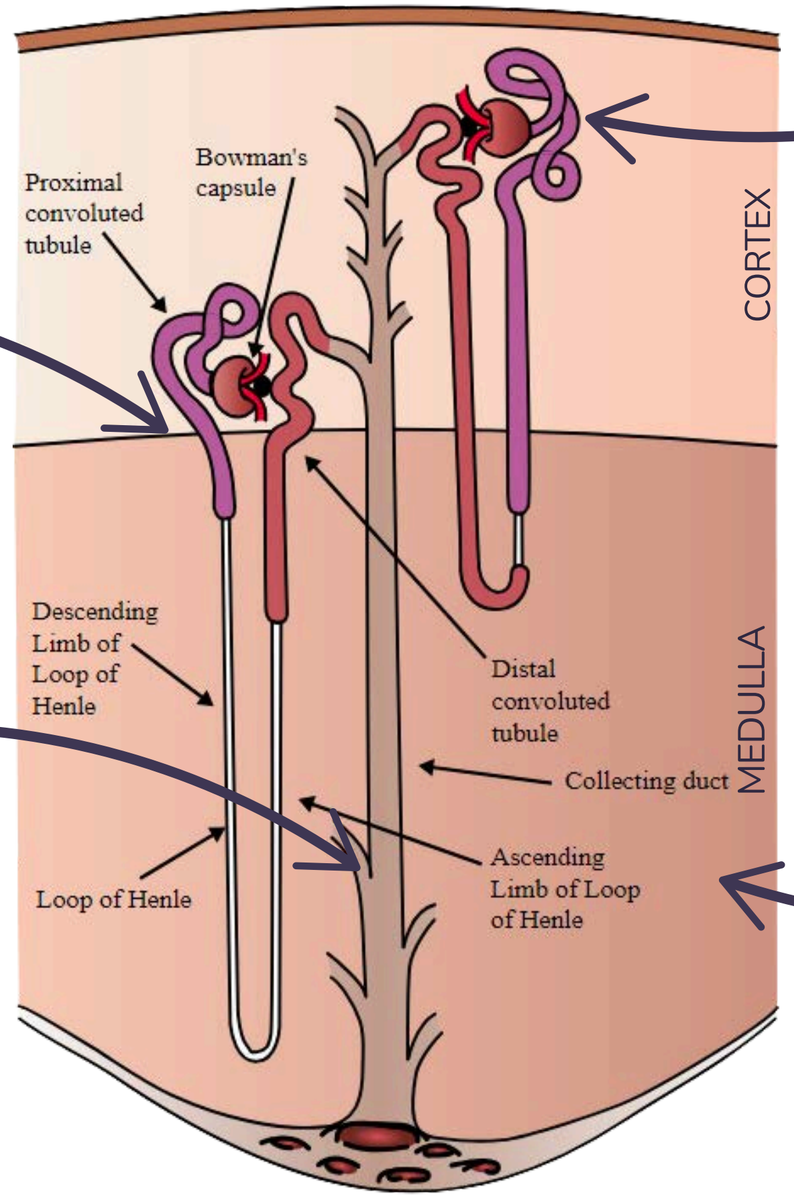
Haemolysis

Intravascular haemolysis depletes nitric oxide and promotes a pro-inflammatory state. This can lead to endothelial damage

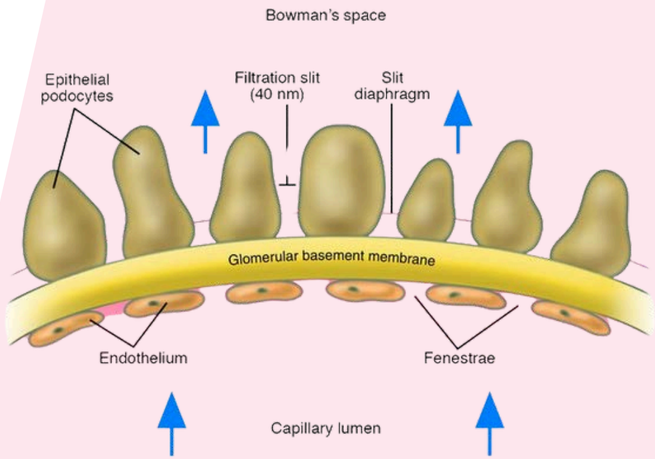
(VERY BASIC) RENAL NEPHRON PHYSIOLOGY

Loop of Henle and convoluted tubules - resorption/secretion of ions. Blood vessels called the **vasa recta** travel alongside.

Collecting system - resorption of water



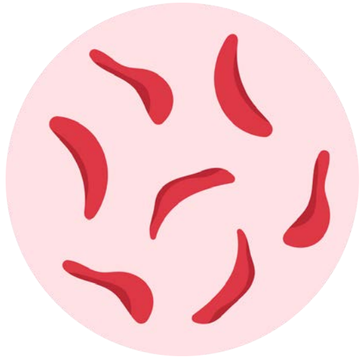
Glomerulus - filters blood into filtrate. Should not include cells or protein



Renal medulla - low pO2, acidotic environment

Nephron - Wikipedia

HOW SICKLE CELLS ACT IN THE KIDNEY



Hypoxic/acidotic conditions and slow blood flow in the renal medulla encourage HbS polymerisation and sickling of red cells, even at low HbS concentrations

Vaso-occlusion in vasa recta leads to recurrent ischaemia-reperfusion injury

Intravascular haemolysis depletes nitric oxide and promotes local vasocontriction and systemic vasodilation

EARLY CHANGES IN SICKLE NEPHROPATHY

Glomerular hypertrophy

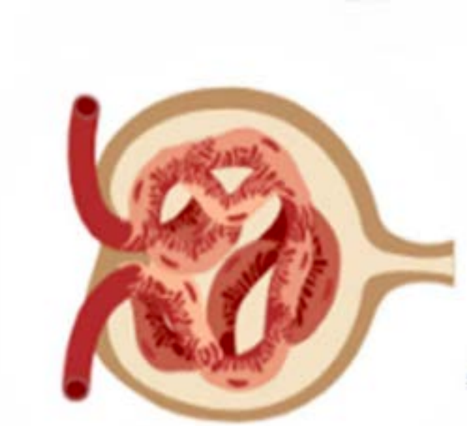
This process begins in infancy.

Increased systemic blood flow results in increased renal blood flow.

“Perfusion paradox”

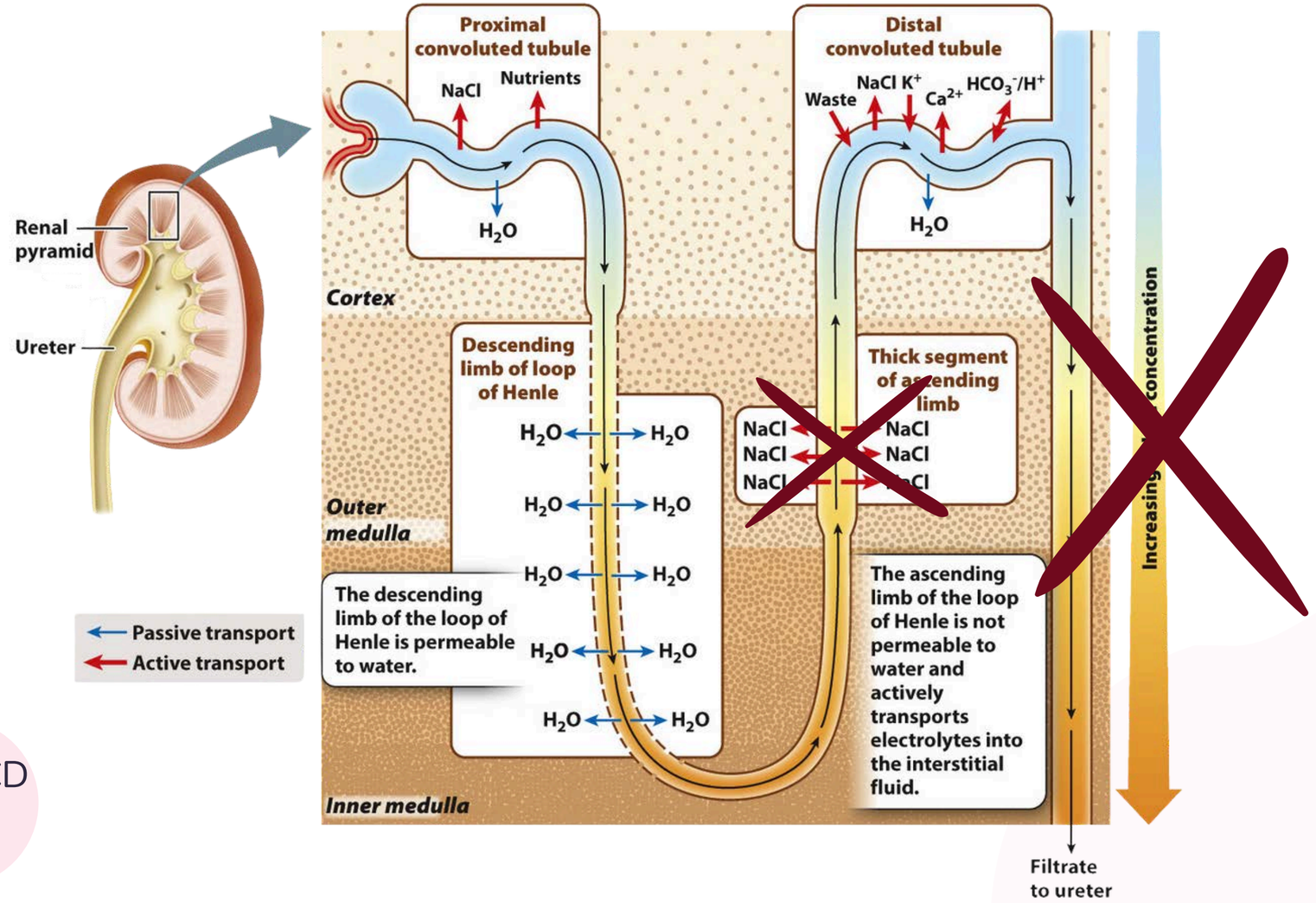
Glomerular hypertension and congestion leads to glomerular hypertrophy.

The reason for this process is not well known, but intermittent hypoxaemia and prostaglandin release from vasa recta ischaemia may be implicated.



Glomerular hypertrophy leads to hyperfiltration and an elevated eGFR - particularly in childhood

URINE CONCENTRATION DEFECTS (HYPOSTHENURIA)

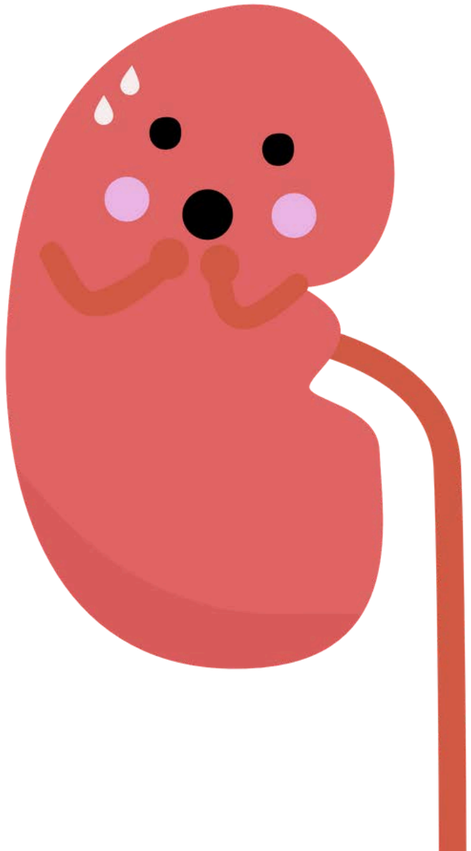


This is near-universal in all SCD patients.

CONSEQUENCES OF HYPERFILTRATION AND HYPOSTHENURIA

Increased urination and risk of enuresis

More filtration and less resorption leads to more urine passing through to the bladder. In children, this can lead to nocturnal enuresis which can persist into teenage years.



Significant risk of dehydration

Patients are at a higher risk of becoming dehydrated. This can increase the risk of sickling, painful crisis and other vaso-occlusive complications.

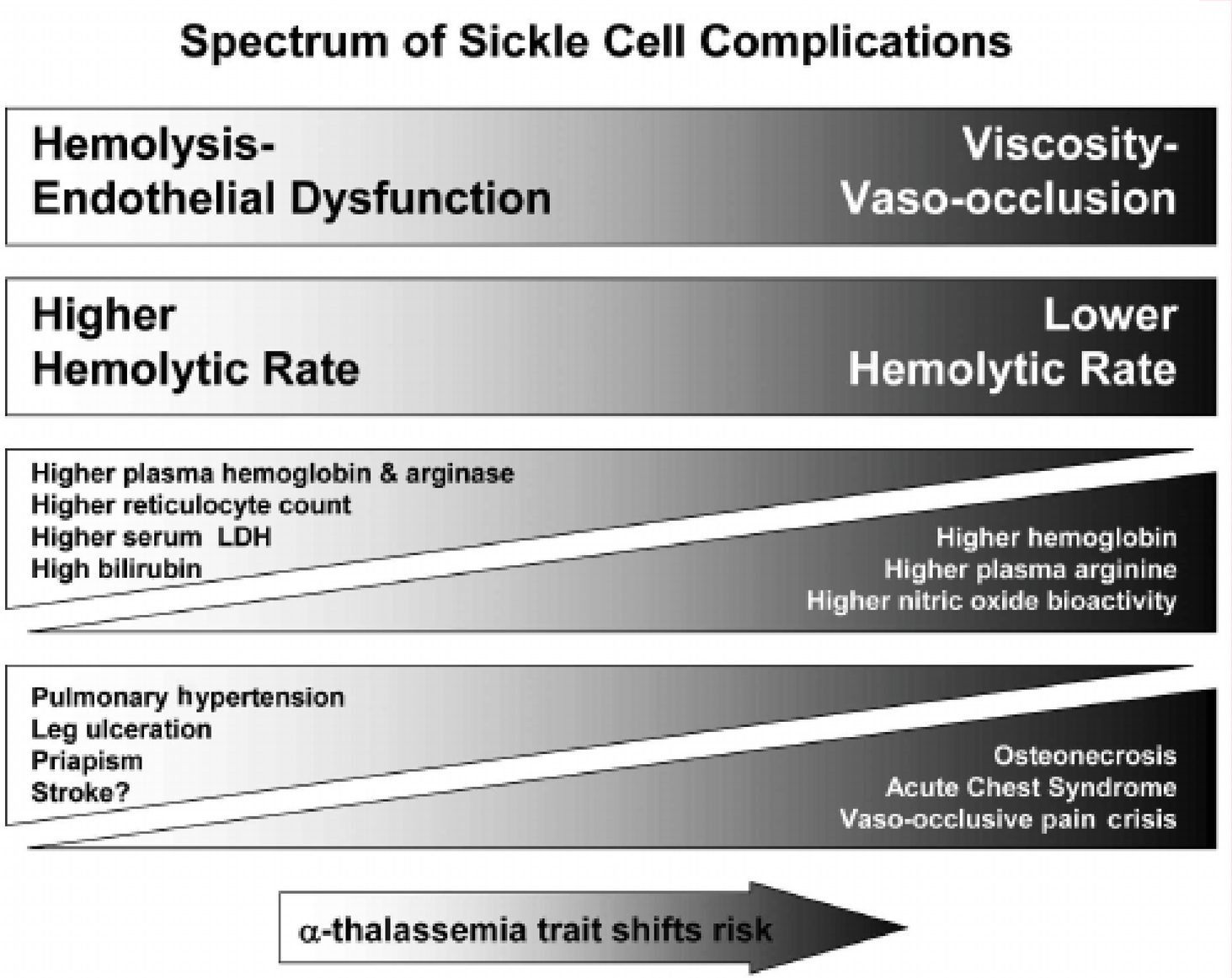
DEVELOPMENT OF ALBUMINURIA

Early glomerular dysfunction and hyperfiltration leads to microalbuminuria.

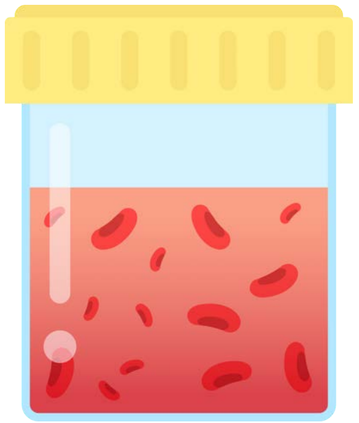
This progresses to macroalbuminuria and frank proteinuria.

Presence of albumin or frank protein in the urine is a marker of glomerular injury or damage resulting from:

- Recurrent vaso-occlusion
- Haemolysis-related vascular damage (alpha-thalassaemia trait protective against albuminuria).


Spectrum of Sickle Cell Complications
Hemolysis-
Endothelial Dysfunction
Viscosity-
Vaso-occlusion
Higher
Hemolytic Rate
Lower
Hemolytic Rate
Higher plasma hemoglobin & arginase
Higher reticulocyte count
Higher serum LDH
High bilirubin
Higher hemoglobin
Higher plasma arginine
Higher nitric oxide bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke?
Osteonecrosis
Acute Chest Syndrome
Vaso-occlusive pain crisis
α-thalassemia trait shifts risk

HAEMATURIA

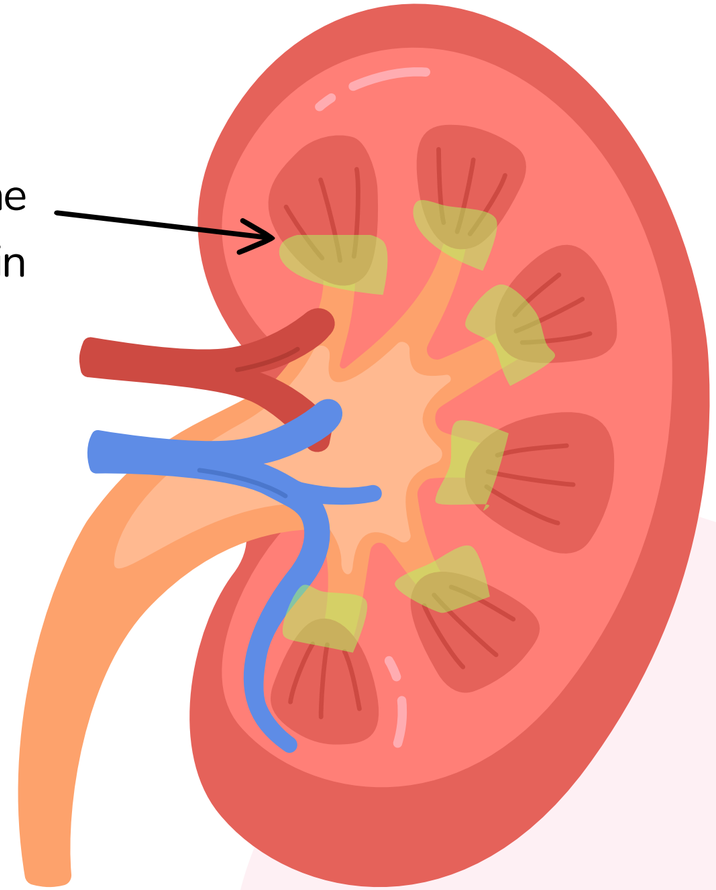


Haematuria (both microscopic and macroscopic) is common and often occurs due to microinfarcts of renal papillae or renal papillary necrosis.

Necrosis occurs due to ischaemic injury and haemolysis-induced pro-inflammatory environment.

Is is usually self-limiting but can cause colicky pain and rarely urinary obstruction.

Renal papillae (highlighted in green)



PATHOPHYSIOLOGY OF PROGRESSIVE SICKLE NEPHROPATHY

Vasa recta dysfunction leads to loss of nephrons

Nephron loss pushes single nephron GFR

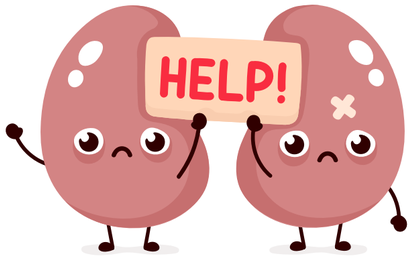
Persistent glomerular hypertrophy causes glomerular scarring and sclerosis

Tubular atrophy

Focal segmental glomerular sclerosis

Interstitial fibrosis

Loss of GFR
(Initially normal and eventually low)



WHAT ABOUT TRAIT?

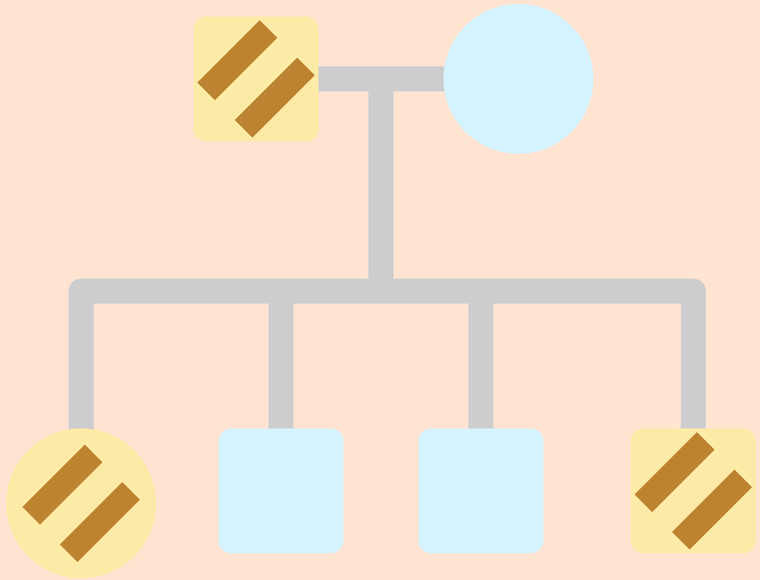
HbAS can cause some sickling in medullary conditions

- Low oxygen partial pressures
- Acidotic
- Dehydration/high osmolality
- Slow blood flow

Haematuria related to papillary necrosis

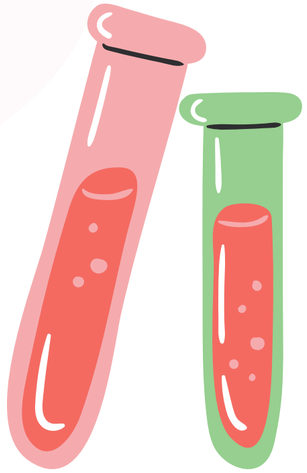
Glomerular hypertrophy and hypothenuria

Renal medullary cell carcinoma



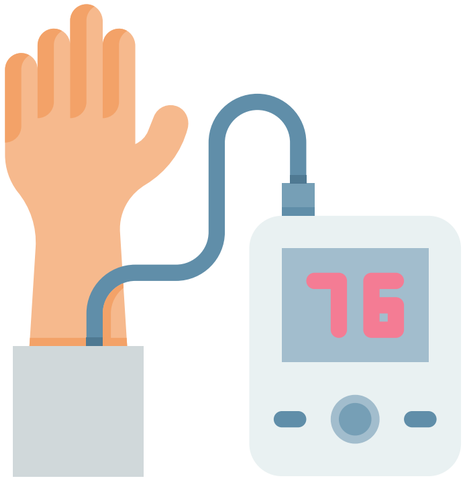
SCREENING FOR RENAL DISEASE

All SCD patients should be screened annually at annual review



Renal function

Urine Dipstick and Protein/Creatinine Ratio



Blood pressure measurement

PCR >50 on two occasions is significant for renal disease

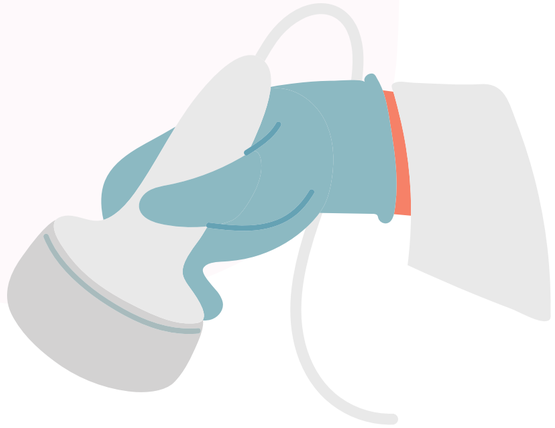
DEFINITION OF CKD

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73 m^2), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

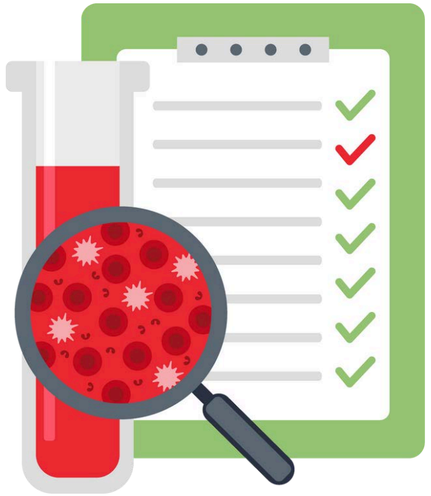
Increasing risk

ACR 30 = PCR 50

IF PROTEINURIA OR FALLING EGFR



Arrange renal ultrasound



Send bloods for complement, ANA, myeloma screen and chronic viral serology

Refer to renal team - consider biopsy

If proteinuria - consider ACEi (see next slide)

RAMIPRIL FOR PROTEINURIA

Mechanism

Ramipril probably works by reducing intraglomerular pressure, therefore reducing permeability to albumin and proteins

Side effects

Patients with SCD run a lower blood pressure, so therefore are more likely to experience postural hypotension.

Unintended benefits

The usual reduction in GFR related to ACEis may improve nocturia symptoms.

OTHER MANAGEMENT OPTIONS

Hydroxycarbamide

Early hydroxycarbamide seems to help to reduce eGFR (therefore reducing hyperfiltration) in babies and children

Transfusion

Transfusion programmes technically reduce sickling - but are understudied in this setting

Kidney transplant

Rarely happens, but has better outcomes than dialysis.

ANY QUESTIONS?