
حمد و سپاس خدای را
حمدی که حدی و مرزی نشناسد
و حسابش به شمار در نیاید
و پایانش نبود.

Sickle cell disease effects on the kidney

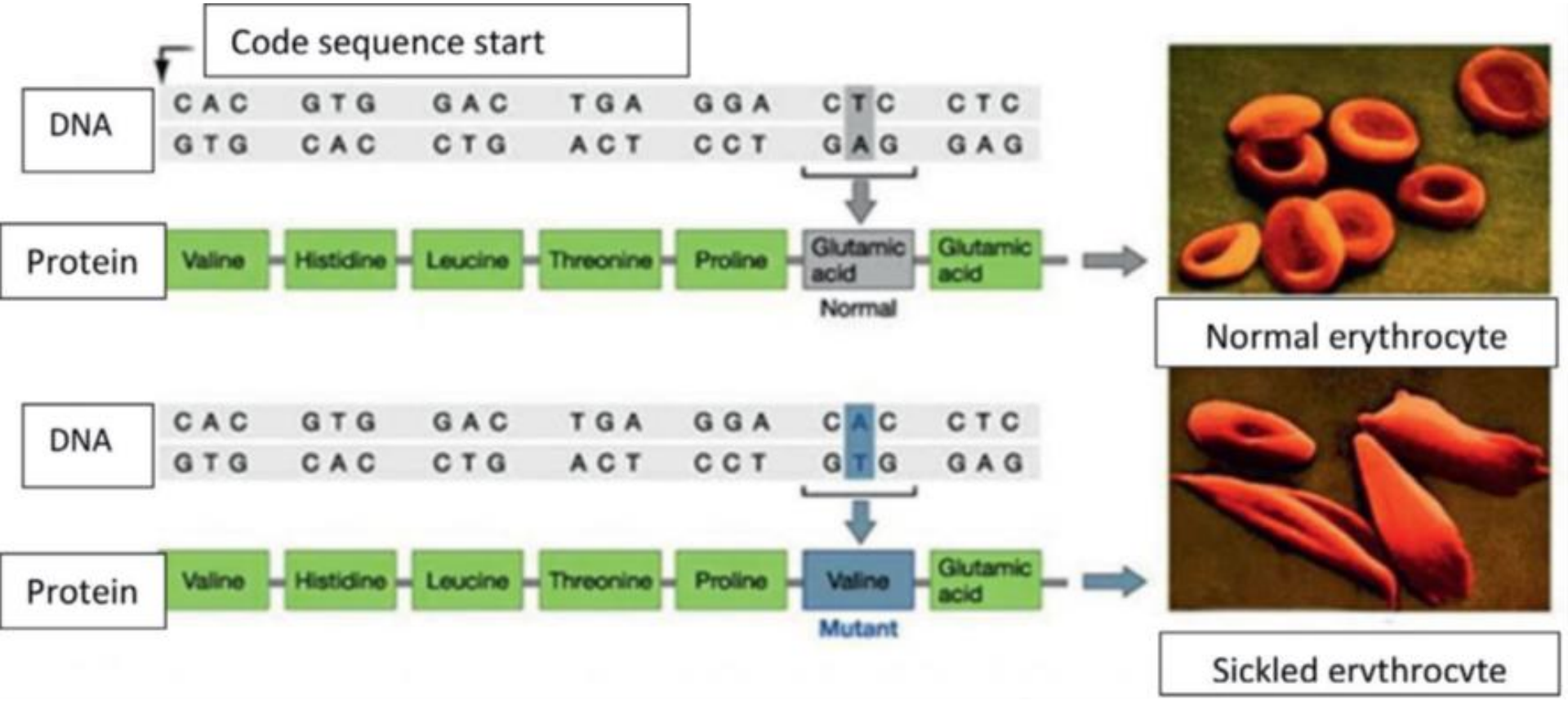
Said peyrovi

Nephrologist

- In 1910, Herrick JB first described sickle cell nephropathy in a black student. He described anemia with elongated sickle-shaped red blood cells, increased urine volume, and decreased urine density. Sickle cell disease (SCD) is a genetically inherited disease that affects many systems and is a clinical condition that occurs when red blood cells contain modified HbS.

HbS is formed by the replacement of glutamine at position 6 at the amino (-NH_2) end of the beta-globin chain with the amino acid valine. It is formed when GTG (Guanine-Tymine-Guanine) replaces GAG (Guanine-Adenine-Guanine) at the base level.

Rumeysa Duyuran and Hülya Çiçek : Investigation of Sickle Cell Nephropathy . Published: 24 January 2024



Kidney abnormalities in SCD

SCD is characterized by the presence of multiple alterations in kidney function, including abnormalities in the proximal and distal tubules (for example, increased reabsorption of phosphate and β2-microglobulin, and increased secretion of uric acid and creatinine), as well as changes in renal haemodynamics that promote hyperfiltration and glomerular damage.

Box 1 | Renal manifestations of sickle cell disease

Alterations in renal haemodynamics

- Increased renal blood flow rate
- Increased renal plasma flow rate
- Increased glomerular filtration rate
- Decreased renal vascular resistance
- Decreased filtration fraction
- Decreased medullary perfusion

Renal and glomerular enlargement

Hyperfunction of the proximal tubule

- Increased reabsorption of phosphate and β2-microglobulin
- Increased secretion of creatinine and uric acid
- Increased transport maximum of para-aminohippurate

Glomerulopathies

- Focal segmental glomerulosclerosis
- Membranoproliferative glomerulonephritis
- Thrombotic microangiopathy

Tubular deposits of iron

Chronic tubulointerstitial disease

Impaired function of the distal nephron

- Decreased urinary concentrating ability
- Partial distal renal tubular acidosis
- Impaired renal potassium excretion

Increased susceptibility to acute kidney injury

Chronic kidney disease and its progression to end-stage renal disease

Haematuria

Renal papillary necrosis

Increased susceptibility to urinary tract infections

Renal medullary carcinoma

Kidney abnormalities in SCD

Impaired urinary concentration

relative hypoxia, acidosis and hyperosmolarity of the inner renal medulla

ischaemic injury and microinfarction and loss of juxtamedullary nephrons

urinary endothelin 1 (ET1) levels in patients with SCD ↑

Nocturnal enuresis is common in children and young adults with SCD

Kidney abnormalities in SCD

Urinary acidification and Potassium excretion

Defective urinary acidification in SCD manifests similarly to incomplete distal renal tubular acidosis

Impaired distal tubule secretion may result in defective potassium excretion in SCD. These defects occur despite intact aldosterone and renin responses

hyporeninemic hypoaldosteronism

Kidney abnormalities in SCD

Supranormal renal haemodynamics

elevated effective renal plasma flow (ERPF) and GFR

decreased filtration fraction

glomerular hyperfiltration in SCD is commonly defined as estimated glomerular filtration rate (eGFR) >130 ml/min/1.73 m2 in women and >140 ml/min/1.73 m2 in men

Kidney abnormalities in SCD

Impaired glomerular filtration

Albuminuria, is common in SCD

27% of children and young adults, and 68% of older patients with SCD

Albuminuria is more prevalent in patients with HbSS or HbSβ0

urinary albumin-to-creatinine ratio (UACR) increased at a linear rate of 3.5 mg/g per year

FSGS

Kidney abnormalities in SCD

Haematuria

Haematuria is common in SCD but it is typically mild, painless and self-limited

vascular occlusion in the renal medulla

microinfarction-induced papillary necrosis

Mechanisms underlying sickle cell nephropathy

Haemolysis and oxidative stress

HMOX1

A1M-to-haemopexin ratio

ROS

Mechanisms underlying sickle cell nephropathy

Endothelial dysfunction

Soluble vascular endothelial growth factor receptor 1 (sVEGFR1) ↑

Plasma and urinary levels of ET1 correlate positively with albuminuria in SCD and Binding of ET1 to ETA

leads to vasoconstriction, inflammation, mitogenesis, and nociception

Glomerulus:

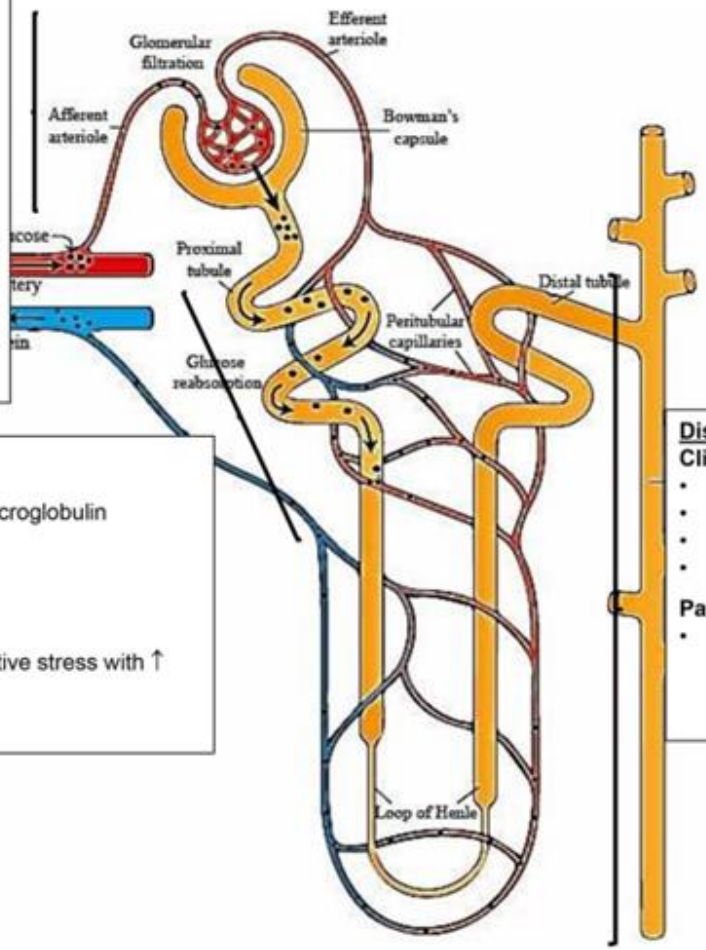
Clinical Complications:

- Albuminuria
- Proteinuria
- Reduced eGFR

Pathophysiology:

- Altered glomerular autoregulation leading to hyperperfusion and mediated by ↑ prostaglandin, NO, ANP
- Endothelial dysfunction, in part from increased ET-1 and sVEGFR1 levels
- Cell-free hemoglobin/heme-mediated oxidative stress with ↑ ROS
- Hypoxia from vaso-occlusion and anemia

Biomarkers: Nephrin, ET-1, sVEGFR1, MCP1



Proximal tubule:

Clinical Complications:

- Increased reabsorption of phosphate, β_2-microglobulin
- Increased secretion of uric acid, creatinine
- Reduced NH_4^+ production

Pathophysiology:

- Hypoxia from vaso-occlusion and anemia
- Cell-free hemoglobin/heme-mediated oxidative stress with ↑ ROS

Biomarkers: KIM1, NAG, CCL2

Distal Nephron:

Clinical Complications:

- Hematuria
- Impaired urinary concentration
- Renal tubular acidosis
- Reduced potassium excretion

Pathophysiology:

- Vaso-occlusion with ischemic injury and microinfarctions resulting in rarefaction of the vasa-recta and papillary necrosis

Genetic modifiers of kidney disease risk

Several genetic modifiers that affect the severity of haemolysis

Replicated gene variants implicated in sickle cell nephropathy

Gene	Gene product	Variants	Effects associated with variant in patients with SCD
HBA1	Haemoglobin subunit α1	α-3.7K deletion α-4.2K deletion	Reduction in albuminuria, higher eGFR and lower risk of CKD progression
APOL1	Apolipoprotein L1, which is a major component of the trypanosome lytic factor complex	G1 (S342G or S342G and I384M substitution) G2 (N388 and Y389 deletion)	Homozygous or compound heterozygous inheritance of *APOL1* G1 & G2 variants: associated with increased risk of urine dipstick-defined proteinuria, higher albuminuria, lower eGFR, higher CKD stage, faster CKD progression and increased risk of kidney failure
HMOX1	Haem oxygenase 1, which is a rate-limiting inducible enzyme that metabolizes haem to biliverdin, carbon monoxide and iron	GT-repeat in promoter region or rs743811	Long GT-tandem repeats (> 25): lower baseline eGFR and higher AKI risk rs743811: lower eGFR, greater albuminuria, higher CKD stage and increased risk of kidney failure
ACKR1	Atypical chemokine receptor 1 (also known as the Duffy antigen receptor 1, which is a receptor for Plasmodium vivax and serves as a chemokine-scavenging receptor	rs2814778	Higher risk of urine dipstick-defined proteinuria and more severe albuminuria

Detection of kidney disease in SCD

Albuminuria

Measuring and estimating GFR

the CKD-EPI equation using cystatin C alone seems to be the optimal choice for estimating GFR in adults

The CKiD Schwartz formula might therefore be the best current option for estimating GFR in children.

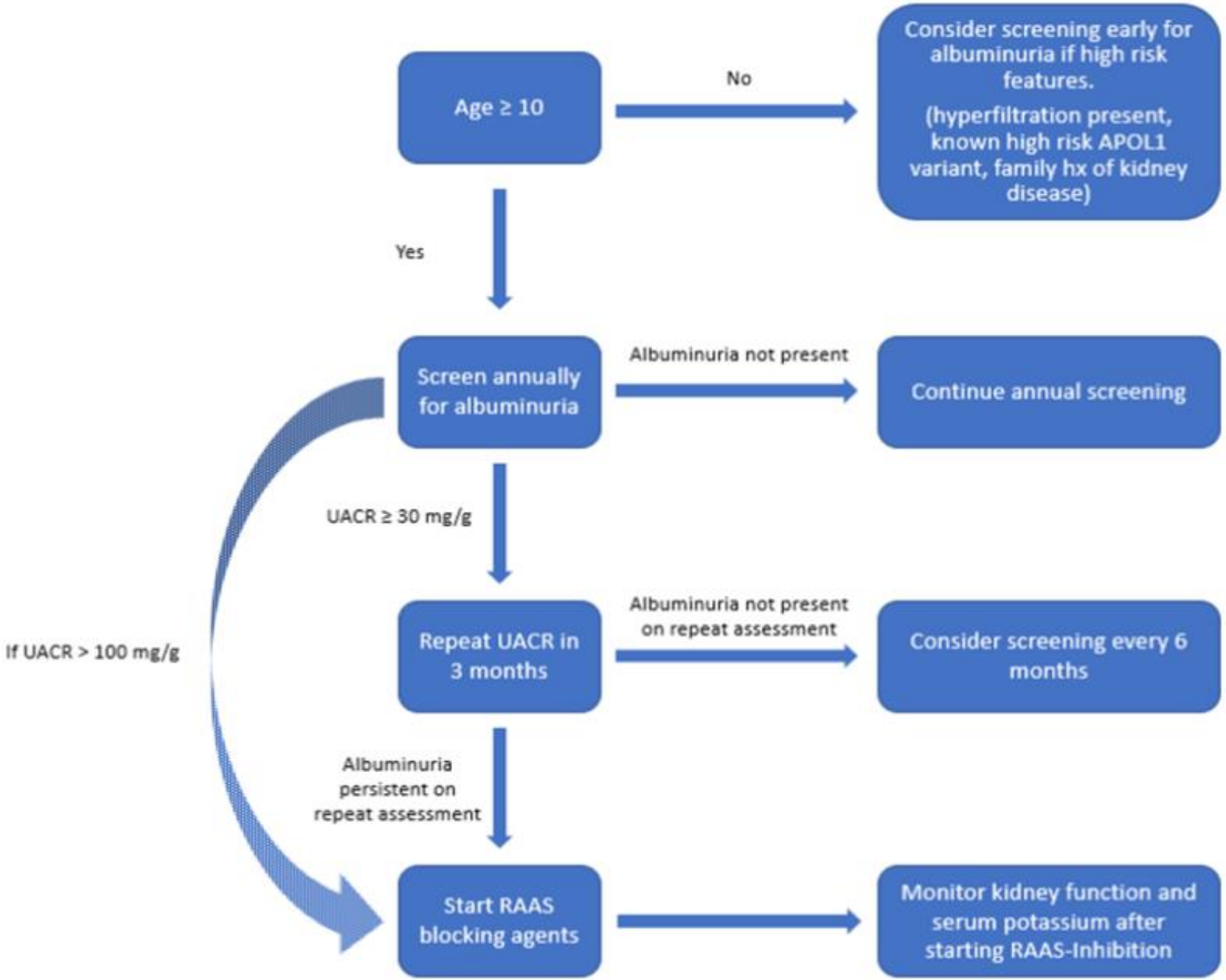
kidney biopsy

Biomarkers of kidney disease

endothelial dysfunction (ET1 and sVEGFR1)

glomerular (nephrin)

tubular injury (KIM1 and NAG) and inflammation (CC-chemokine ligand 2 (CCL2)


Age ≥ 10
No
Consider screening early for albuminuria if high risk features.
(hyperfiltration present, known high risk APOL1 variant, family hx of kidney disease)
Yes
Screen annually for albuminuria
Albuminuria not present
Continue annual screening
UACR ≥ 30 mg/g
Repeat UACR in 3 months
Albuminuria not present on repeat assessment
Consider screening every 6 months
If UACR > 100 mg/g
Albuminuria persistent on repeat assessment
Start RAAS blocking agents
Monitor kidney function and serum potassium after starting RAAS-Inhibition

Treatment of sickle cell nephropathy

SCD-specific therapy

Kidney-specific therapy

Novel therapeutic options

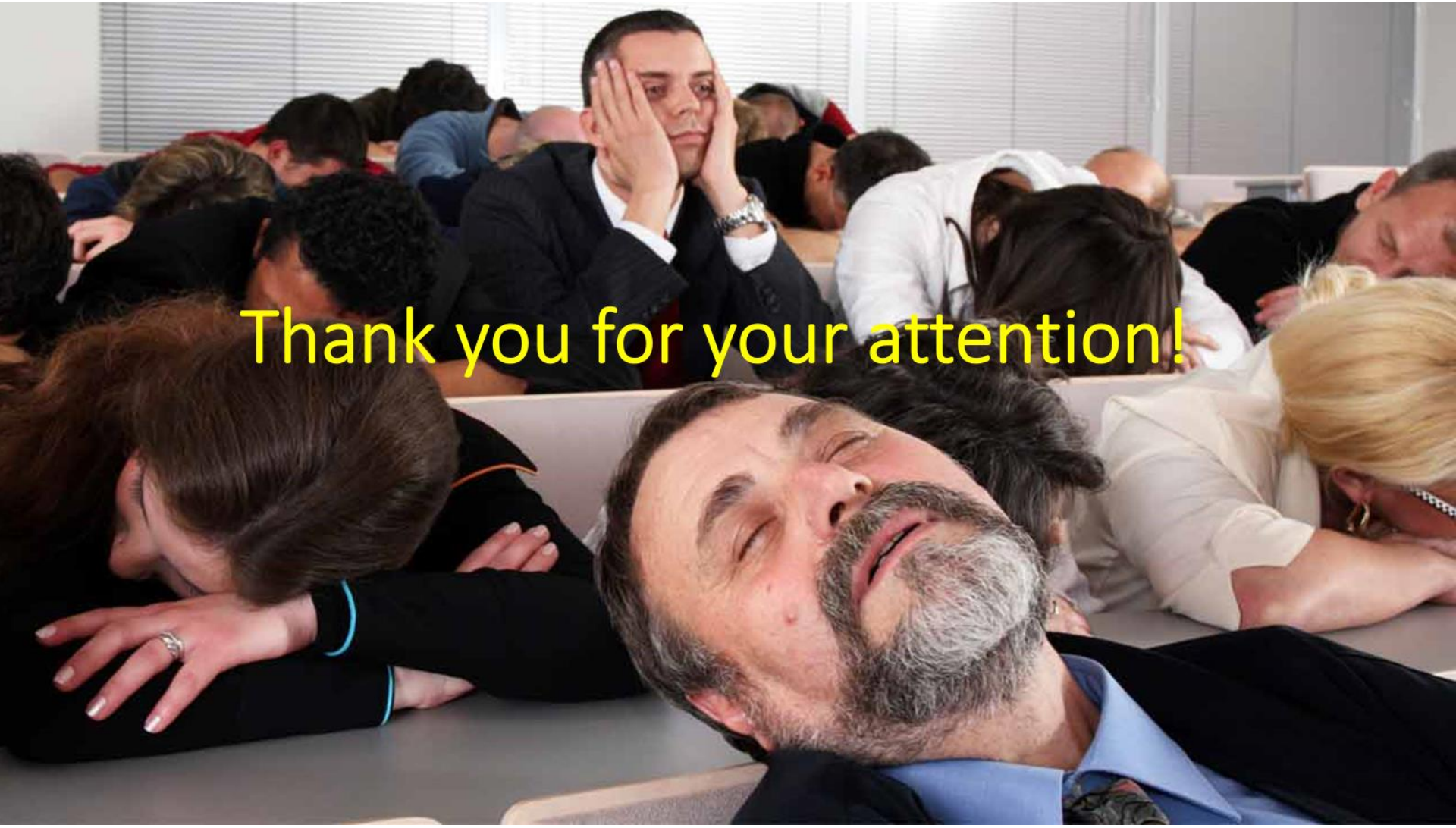
Management of advanced CKD in SCD

Anti-hypertensive therapy

Diuretic use

Erythropoiesis-stimulating agents

Iron chelation therapy


Thank you for your attention!