• History
• Pathophysiology
• Renal manifestations
• Treatment
• New developments
• Sickle cell trait
SCD has been known in Africa for 100’s of yrs
First described in western literature in 1910 by James Herrick
Linus Pauling and Harvey Itano in 1948 demonstrated by protein electrophoreisis that hb in SCD was different
In 1956, Vernon Ingram sequenced S hemoglobin – 1st genetic disease whose molecular basis was known
PATHOPHYSIOLOGY

- Single base pair substitution in the B-globin gene at position 6 changing from glutamic acid to valine
- Hemoglobin S undergoes polymerization when oxygen concentration is reduced causing sickling
- Hb SS, SC, Sb-thal are called SCD
CURRENT MODEL OF SCAN

Fig 1 The current model of sickle cell nephropathy. The environment of the renal medulla is hypertonic, hypoxic, and acidic, causing reversible sickling of red blood cells (RBC). The RBC sickling results in vessel occlusion, ischemia, and microinfarction of the vasa recta. This destruction is believed to trigger the release of vasodilating substances (such as prostaglandins and nitric oxide) that feed back to the glomerulus causing hyperfiltration. With time, hyperfiltration injury leads to glomerulosclerosis, proteinuria, and eventual renal failure.
RENAL ABNORMALITIES

- Urinary concentration defects
- Impaired urinary acidification
- Cortical scarring
- Renal medullary ca
- Proteinuria
- ESRD
RENAL HEMODYNAMICS IN SCD

- Response to ischemia in murine model C57BL/6 homozygous for b-globin deletion
- Effect of 22.5min ischemia on GFR, RBF, FF, changes in renal histology and expression of MAPK/Akt signaling proteins

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Fig. 1. Renal hemodynamics: glomerular filtration rate (GFR) and renal blood flow (RBF). A: total GFR was determined by clearance techniques in wild-type (WT) and sickle mice (SCD) following bilateral renal ischemia-reperfusion (IR) for 22.5 min or after sham ischemia (Sham). B: RBF was determined by a flow probe placed on the left renal artery following bilateral renal ischemia for 22.5 min (IR) or after Sham; n = 5 and n = 4–5 for WT and SCD mice subjected to IR, respectively, and n = 4 for both WT and SCD mice subjected to Sham. *P < 0.05 vs. WT mice subjected to IR for that index.
Fig. 3. Renal hemodynamics: renal plasma flow (RPF) and filtration fraction (FF). A: RPF was calculated as RBF × (100 – hematocrit)/100 from values of these indices determined during studies of renal hemodynamics undertaken following bilateral IR for 22.5 min or after Sham. B: FF of the kidney was calculated as single kidney GFR/RPF from these indices; n = 5 and n = 4 for WT and SCD mice subjected to IR and n = 4 for both WT and SCD mice subjected to Sham. *P < 0.05 vs. WT mice subjected to IR for that index.
Fig. 2. Renal hemodynamics: mean arterial pressure (MAP) and renal vascular resistance (RVR). A: MAP was determined during studies of renal hemodynamics undertaken following bilateral renal IR for 22.5 min or after Sham. B: RVR was calculated as MAP/RBF from values of these indices determined during renal hemodynamic studies undertaken following bilateral renal IR for 22.5 min or after Sham; n = 5 and n = 4–5 for WT and SCD mice subjected to IR, and n = 4 for both WT and SCD mice subjected to Sham. *P < 0.05 vs. WT mice subjected to IR for that index. #P < 0.05 vs. WT mice subjected to Sham for that index.
Fig. 4. Histological examination of the renal cortex in WT and SCD mice following renal hemodynamic studies. A: renal cortex in WT mice after ischemia (×100). B: renal cortex in SCD mice after ischemia (×100). C: renal cortex in WT mice after ischemia (×400). D: renal cortex in SCD mice after ischemia (×400). All sections were stained with hematoxylin and eosin. As shown in these representative sections, the vasculature and glomeruli were congested in SCD mice (B and D) following ischemia; such congestion was not observed in the kidney in WT mice (A and C). The vasculature and glomeruli in the kidney in SCD mice were variably congested after ischemia (B), and D illustrates severe congestion in the vasculature and glomeruli in SCD mice after ischemia. Renal tubules showed no injury in WT and SCD mice.
**ERK1/2 and p-ERK1/2**

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<th>WT</th>
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<td>Sham</td>
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<tr>
<td>p-ERK 1/2</td>
<td>β-Actin</td>
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**JNK and p-JNK**

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<td>IR</td>
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<tr>
<td>p-JNK</td>
<td>β-Actin</td>
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Fig. 5. Western blot analysis for the expression of ERK1/2 in WT and SCD mice following IR injury or Sham. *Top:* expression of phospho-ERK1/2 in the kidney in WT and SCD mice following renal IR or Sham. *Bottom:* expression of ERK1/2 in the kidney in WT and SCD mice following renal IR or Sham. For each Western blot analysis, each lane represents protein extracted from a single kidney of an individual mouse; evaluation of adequacy of loading was provided by immunoblotting for β-actin.

Fig. 6. Western blot analysis for the expression of JNK in WT and SCD mice following IR injury or Sham. *Top:* expression of phospho-JNK in the kidney in WT and SCD mice following renal IR or Sham. *Bottom:* expression of JNK in the kidney in WT and SCD mice following renal IR or Sham. For each Western blot analysis, each lane represents protein extracted from a single kidney of an individual mouse; evaluation of adequacy of loading was provided by immunoblotting for β-actin.

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Fig. 9. Expression of inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) mRNA following IR or Sham in WT and SCD mice. iNOS mRNA (A) and eNOS mRNA (B) were determined by quantitative real-time RT-PCR in the kidney in WT and SCD mice following renal IR or Sham. For either gene, n = 6 in WT and SCD mice subjected to Sham, and n = 9 and n = 8 in WT and SCD mice, respectively, subjected to IR. *P < 0.05 SCD mice vs. WT mice subjected to IR for that gene.
ET-1

Fig. 10. Expression of endothelin-1 (ET-1) mRNA following IR or Sham in WT and SCD mice. ET-1 mRNA was determined by quantitative real-time RT-PCR in the kidney in WT and SCD mice following renal IR or Sham; n = 6 in WT and SCD mice subjected to Sham, and n = 9 and n = 8 in WT and SCD mice, respectively, subjected to IR.
TNF-ALPHA MCP-1

Fig. 11. Expression of TNF-α and MCP-1 mRNA following IR or Sham in WT and SCD mice. TNF-α mRNA (A) and MCP-1 mRNA (B) were determined by quantitative real-time RT-PCR in the kidney in WT and SCD mice following renal IR or Sham. For either gene, n = 6 in WT and SCD mice following Sham, and n = 9 and n = 8 in WT and SCD mice, respectively, following IR.

*P < 0.05 SCD mice vs. WT mice following IR for that gene.
CONCLUSIONS

- Significant decrease in RBF, GFR, FF
- Increased vascular resistance in SCD mice vs WT
- Histology shows vascular congestion
- Phosphorylated forms of signaling protein was markedly altered in sickle mice after ischemia
URINARY CONCENTRATING ABILITY

- Progressively lost with age, irreversible after 15yrs
- Maximum urine osmolality 400-450mosm/kg

- Overnight fast followed by water loading 20ml/kg
- U osm was lower in SCA than normal-414mosm/kg vs 911mosm/kg
- Indomethacin caused 200 % increase in U osm in SCA

GLOMERULAR HYPERFILTRATION

**Figure 1.** Distribution of patients with SS disease according to GFR.

**Figure 2.** Distribution of patients with SS disease with hyperfiltration according to albuminuria. μAlb, microalbuminuria; Malb, macroalbuminuria.

Table 4. Characteristics of SCA patients with hyperfiltration alone (n = 63) and normal GFR

<table>
<thead>
<tr>
<th></th>
<th>Hyperfiltration Alone (n = 63)</th>
<th>Normal GFR (n = 56)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>21.9</td>
<td>27.1</td>
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<tr>
<td>BMI, kg/m²</td>
<td>20.6</td>
<td>20.5</td>
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<tr>
<td>Gender, % male</td>
<td>40</td>
<td>30</td>
<td>0.23</td>
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<tr>
<td>eGFR (MDRD), ml/min per 1.73 m²</td>
<td>160</td>
<td>104</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR (Cockroft), ml/min per 1.73 m²</td>
<td>162</td>
<td>115</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>8.5</td>
<td>9.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Bilirubin, IU/L</td>
<td>57</td>
<td>42</td>
<td>0.004</td>
</tr>
<tr>
<td>HbF, %</td>
<td>5.5</td>
<td>8.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>702</td>
<td>360</td>
<td>0.16</td>
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<tr>
<td>No thalassemia, %</td>
<td>62</td>
<td>40</td>
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<tr>
<td>LDH, IU/L</td>
<td>397</td>
<td>360</td>
<td>0.09</td>
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<tr>
<td>Reticulocyte count 10³/mm³</td>
<td>335</td>
<td>298</td>
<td>0.07</td>
</tr>
</tbody>
</table>

BMI, body mass index; Hb, hemoglobin; LDH, lactate dehydrogenase.

*aGroup of homozygous SCA patients defined on the following criteria: no albuminuria and an eGFR >60 ml/min per 1.73 m².
HEMATURIA

- Seen in both scd and sct
- Sec to sickling of erythrocytes in vasa recta results in increase bld viscosity, microthrombi and ischemic necrosis
- Predominately bleeding from left kidney more than right
PROTEINURIA

- 300 pts with SCA
- 184 with HbSS
- Prevalence of microalbuminuria - 40% in all ages
- Macroalbuminuria – increased prevalence with age reaching 40% >40yrs

*Figure 2. Age and the prevalence of albuminuria in adults with sickle cell hemoglobinopathies. □, normoalbuminuria; □, microalbuminuria; ■, macroalbuminuria.*

ACE INHIBITORS IN SCAD

- Prospective study of 10 out of 381 patients with SCD
- Prevalence of proteinuria and renal insufficiency and effects of ACEI
- Renal biopsy, GFR, RPF and protein excretion before, during and after ACEI use.
Figure 3. Urinary Protein Excretion in 10 Patients with Sickle Cell Disease at Base Line, after Two Weeks of Enalapril, and at Follow-up, Two to Three Weeks after Enalapril Was Stopped. There was a significant (P<0.001) decrease in protein excretion during enalapril administration.
ACE INHIBITORS IN SCAD

Figure 4. Glomerular Filtration Rate and Effective Renal Plasma Flow at Base Line, after Two Weeks of Enalapril, and at Follow-up, Two to Three Weeks after Enalapril Was Stopped.

Figure 2. Glomerular Areas Measured in Renal-Biopsy Specimens from Patients with Sickle Cell Disease and Control Patients.
CONCLUSIONS

- 7% had renal insufficiency
- 25% had proteinuria
- Biopsies showed glomerular enlargement and FSGS
- Glomerular surface was twice that of control
- ACEI decreased proteinuria >50% suggesting glomerular capillary hypertension as factor in SCAN.
HYDROXYUREA- MSH TRIAL

- Use in acute sickle cell crisis- RCT - multicenter randomized double blinded placebo control to test use in pts with painful crisis
- 299 patients (90% power)
- Hydroxyurea 15mg/kg/day upto 35mg/kg/day
- Trial stopped early due to 50% reduction in crisis rate in study arm

*Controlled clin trial 1995;16:432-446*
FOLLOW UP TO MSH TRIAL

- Prospective 17.7 years follow up (1992-2009)
- 43.1% of the original cohort died
- 17% had renal dysfunction
- 87% of death occurred in patients not exposed to hydroxyurea and <5yrs exposure
SICKLE CELL DISEASE AND TRANSPLANT

- 1 yr graft survival similar to other ESRD but 3yr graft survival lower (48% vs 60%)
- Patient survival lower compared to other ESRD- 78% vs 90%
- Painful sickle crisis has been associated with use of OKT3
- Recurrence of SCAN has also been reported in transplant kidney

NEWER DEVELOPMENTS

- Role of adenosine in mouse erythrocyte sickling
- Metabolomic profiling revealed elevated adenosine in SCD transgenic mice (p<0.05)
- Looked at effect of 8 wks of PEG-ADA treatment on percentage of sickled RBCs
- Significant reduction of sickled rbc’s and reticulocytes

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SICKLE CELL TRAIT

- SCT found in approx 300 million people
- SCT has been associated with exercise related deaths, splenic infarcts, hematuria, hyposthenuria, venous thromboembolism, fetal loss and renal medullary cancer
RENAL MEDULLARY CARCINOMA

- Exclusively associated with sickle cell status
- More common in SCT and HbSC disease
- 1st described in case series of 34 pts out of which 33 had SCT.
- Approx 120 cases reported only 1 case not associated with sickling status
- Aggressive tumor with median survival 15 wks
THANK YOU