Renal complications of sickle cell disease

Academy for Sickle Cell and Thalassaemia
10th Anniversary Conference

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The kidney is a very vascular organ.
Blood supply to the renal medulla is sluggish and poorly oxygenated.

- Oxygen tension: 50 mmHg (Cortex), 10 mmHg (Medulla)
- pH: 7.4 (Cortex), 6.4 (Medulla)

- Prostaglandin release
- Endothelin-1
- NO bioavailability

Interstitial osmolarity

Cortex

Medulla

Proximal convoluted tubule
Glomerulus
Distal convoluted tubule
Collecting duct
Loop of Henle
The renal microvasculature is destroyed in sickle cell disease

Normal kidney  Sickle cell disease

Clinical manifestations
Clinical manifestations

Increased GFR from early childhood to young adulthood (125 vs 91 ml/min)

Decreasing GFR from the fourth decade onwards
Clinical manifestations

Increased GFR from early childhood to young adulthood (125 vs 91 ml/min)

Decreasing GFR from the fourth decade onwards

Microalbuminuria leading to proteinuria
Prevalence of microalbuminuria increases with age

**HbSS + HbSβ0**

**HbSC**

*Day TG, Drasar ER et al, Haematologica, 2012 Feb;97(2):201-5*
Clinical manifestations

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Supranormal Proximal tubular function leading to hyperphosphataemia and increased creatinine secretion
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Impairment of distal hydrogen ion and potassium secretion
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Diminished concentrating ability (hyposthenuria)
**Clinical manifestations**

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Microalbuminuria leading to proteinuria

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Diminished concentrating ability (hyposthenuria)
Causes of haematuria in patients with SCD

- Papillary necrosis: Rare
- Medullary carcinoma: Extremely Rare

Common in patients with HbSS and HbAS
Clinical manifestations

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Impairment of distal hydrogen ion and potassium secretion

Diminished concentrating ability (hyposthenuria)

Renal cyst formation

Haematuria
Most adults develop some of the manifestations of sickle cell nephropathy, so why do only some progress?

### Risk factors for progression

<table>
<thead>
<tr>
<th>Severe sickle phenotype</th>
<th>Genetic modifiers</th>
<th>Another renal insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent admissions</td>
<td>Alpha globin genotype</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Recurrent acute kidney injury</td>
<td>Other genetic modifiers</td>
<td>Diabetes</td>
</tr>
<tr>
<td>High levels of haemolysis</td>
<td></td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood borne viruses</td>
</tr>
</tbody>
</table>
### Table 1A. Relationship of hemolytic parameters to ACR in HbSS + HbSβ⁰ group.

<table>
<thead>
<tr>
<th>Hemolytic parameters</th>
<th>SD</th>
<th>% change</th>
<th>Degree of albuminuria</th>
<th>Uncorrected for covariates</th>
<th>Corrected for covariates</th>
<th>Microalbuminuria</th>
<th>P value</th>
<th>OR (95%CI)</th>
<th>P value</th>
<th>Microalbuminuria</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retics (x10⁹/L)</td>
<td>131.7</td>
<td>11.0</td>
<td>(1.8, 21.0)</td>
<td>0.02</td>
<td>0.57 (0.49, 0.64)</td>
<td>0.06</td>
<td>6.6</td>
<td>(-3.3, 17.4)</td>
<td>0.2</td>
<td>-20.0 (-29.7, -8.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>1.4</td>
<td>-17.8</td>
<td>(-26.9, -7.6)</td>
<td>0.0005</td>
<td>0.32 (0.24, 0.41)</td>
<td>0.00002</td>
<td>40.8</td>
<td>(25.5, 58.0)</td>
<td>&lt;0.00001</td>
<td>40.8 (25.5, 58.0)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>161.6</td>
<td>45.5</td>
<td>(30.8, 61.8)</td>
<td>&lt;0.00001</td>
<td>0.72 (0.64, 0.78)</td>
<td>&lt;0.00001</td>
<td>51.6</td>
<td>(26.3, 82.1)</td>
<td>&lt;0.00001</td>
<td>51.6 (26.3, 82.1)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>0.6</td>
<td>57.7</td>
<td>(32.5, 87.3)</td>
<td>&lt;0.00001</td>
<td>0.67 (0.53, 0.78)</td>
<td>0.007</td>
<td>-25.2</td>
<td>(-44.0, -0.2)</td>
<td>0.03</td>
<td>-25.2 (-44.0, -0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>RBC Hb/RET Hb</td>
<td>0.5</td>
<td>-26.3</td>
<td>(-42.0, -8.3)</td>
<td>0.01</td>
<td>0.21 (0.07, 0.48)</td>
<td>&lt;0.00001</td>
<td>0.00003</td>
<td>-48.2 (-60.6, -31.7)</td>
<td>&lt;0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC Hb</td>
<td>0.2</td>
<td>-41.1</td>
<td>(-54.0, -24.7)</td>
<td>&lt;0.00001</td>
<td>0.05 (0.01, 0.20)</td>
<td>0.007</td>
<td>-29.0</td>
<td>(-14.2, 8.33)</td>
<td>0.7</td>
<td>-29.0 (-14.2, 8.33)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

### Table 1B. Relationship of hemolytic parameters to eGFR in HbSS + HbSβ⁰ group.

<table>
<thead>
<tr>
<th>Hemolytic parameters</th>
<th>SD</th>
<th>Absolute change per SD (95%CI)</th>
<th>P value</th>
<th>Corrected for covariates</th>
<th>Absolute change per SD (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retics (x10⁹/L)</td>
<td>131.7</td>
<td>5.1 (2.69, 7.55)</td>
<td>&lt;0.00001</td>
<td></td>
<td>7.7 (5.13, 10.2)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>1.4</td>
<td>-2.23 (-4.38)</td>
<td>0.3</td>
<td></td>
<td>0.2 (-3.22, 3.52)</td>
<td>0.5</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>161.6</td>
<td>-2.7 (-5.72, 0.25)</td>
<td>0.2</td>
<td></td>
<td>-2.2 (-5.25, 0.82)</td>
<td>0.1</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>0.6</td>
<td>2.3 (-4.4, 7.04)</td>
<td>0.2</td>
<td></td>
<td>5.1 (0.28, 9.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>RBC Hb/RET Hb</td>
<td>0.5</td>
<td>-11.0 (-19.29, -2.65)</td>
<td>0.003</td>
<td></td>
<td>-8.6 (-18.69, 1.55)</td>
<td>0.1</td>
</tr>
<tr>
<td>RBC Hb</td>
<td>0.2</td>
<td>-2.2 (-11.86, 7.37)</td>
<td>0.8</td>
<td></td>
<td>-2.9 (-14.2, 8.33)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Day TG, Drasar ER et al, Haematologica, 2012 Feb;97(2):201-5*
Co-inheritance of alpha-thalassaemia protects patients with SCD from developing albuminuria

HbSS + HbSβ^0

Combining genetic modifiers can help to stratify patients for risk of progression

- Homozygosity or compound heterozygosity for APOL1 G1/G2 is observed in 10-15% of African Americans and is the strongest genetic association for CKD.
- APOL1 G1/G2 is also associated with proteinuria and albuminuria in SCA patients.
- Alpha-thalassemia is present in about one-third of SCA patients and is associated with reduced hemolysis and protection from albuminuria.
- A polymorphism in BCL11A leads to higher fetal hemoglobin (HbF) levels, reduced hemolysis and amelioration of SCA-related complications.

*Saraf SL et al, Haematologica September 2016 ePub ahead of print : haematol.2016.154153*
How should we investigate patients with evidence of chronic kidney disease in the outpatient clinic?
Recommended investigations for patients with proteinuria

1. Immunology for lupus nephritis
   - Autoantibodies
   - Double-stranded DNA antibodies
   - Complement levels

2. Virus serology
   - HIV
   - Hepatitis B
   - Hepatitis C
   - HPV B19 (if new-onset nephrotic syndrome or recent transient pure red cell aplasia)

3. Myeloma screen (if > 40 years old)

4. Renal tract ultrasound scan

5. Consider renal biopsy if any of 1-3 is positive or acute onset nephrotic syndrome.
Recommended investigations for patients with haematuria

1. Renal tract ultrasound scan

2. Urine cytology

3. CT urogram

4. Immunology for lupus nephritis
   - Autoantibodies
   - Double-stranded DNA antibodies
   - Complement levels

5. Consider cystoscopy

6. Consider renal biopsy if haematuria is present in combination with proteinuria and the above investigations are negative or if 4 is positive
Who should be referred to a nephrologist?

All patients with proteinuria and a positive nephritic screen including:

- Autoantibodies
- Complement levels
- Double-stranded DNA levels
- HIV screen

Anyone with rapid onset nephrotic syndrome (consider parvovirus B19 infection)

Anyone with declining renal function (eGFR<60 ml/min)
Management of sickle cell nephropathy

Treatments for SCD

- Hydroxycarbamide
- Transfusion Therapy (intermittent or regular)
- Haemopoietic cell transplantation in childhood

Specific treatments for sickle cell nephropathy

- Adequate hydration
- Control of blood pressure if hypertensive
- ACE inhibitors/ARB
- Erythropoietin therapy (+hydroxyurea)
- Dialysis
- Transplantation
Evidence for the use of ACEI and ARB in sickle cell nephropathy

Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease (Review)

Sasongko TH, Nagalla S, Ballas SK

Cochrane Database Syst Rev. 2013 Mar 28;(3):

Table 2. Albumin Excretion per Hour in Captopril and Placebo Groups at Baseline and at 6 Months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Captopril (n = 12)</th>
<th>Placebo (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mg/day)</td>
<td>121 ± 66</td>
<td>107 ± 86</td>
<td>0.67</td>
</tr>
<tr>
<td>6 months (mg/day)</td>
<td>76 ± 45</td>
<td>125 ± 114</td>
<td>0.19</td>
</tr>
<tr>
<td>Absolute change (mg/day)</td>
<td>−45 ± 23</td>
<td>+18 ± 45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percentage change (%)*</td>
<td>−37 (−11, −72)</td>
<td>+17 (+2, +52)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.
* Mean difference (95% confidence interval).

A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia.
Response to ACE inhibition in 7 patients with SCD at Kings
Hydroxycarbamide and exchange transfusion
No RCTs for the use of HU/HC in adults to treat SCN

Glomerular filtration rate at baseline and then after 3 years of treatment with hydroxyurea at maximum tolerated dose.
A case study illustrating how HC can be useful in managing SCN

Mr O

Started Hydroxycarbamide and an ACE inhibitor

Stopped Hydroxycarbamide

Re-started Hydroxycarbamide
Odumade, Oluwunso Oluwemi

Estimated GFR (mL/min)

Haemoglobin S % (HbS) (%)

Right total hip replacement

Stopped HC and Commenced exchange transfusion

July 2013 Birth of twins

Mr O

%HbS

eGFR (ml/min)
**Stopped EBT and commenced HC**

**Commenced Epo therapy**

* * */ **

* * */ **
Prognosis for patients with SCD receiving dialysis is poor

In a retrospective cohort analysis comparing patients with SCD on haemodialysis with an aged-matched (37 years) control group of non-SCD patients receiving Haemodialysis:

• SCD patients were much more likely to die over a 5 year period (46.3 vs 6.4%). Infectious complications and thrombosis of dialysis access was common in the SCD group (no data from the non-SCD control group)

• SCD patients were much less likely to receive a kidney transplant over a 5 year period (26% vs 53.5%)

Transplantation for SCN, our experience in London

Data on 21 patients with SCD (17 HBSS, 3 HBSC) and ESRD from transplant units across London for the past 18 years.

4 have died (19%)

Average age when transplanted: 34
7 from living donors (1 in India, 1 in Pakistan), 14 cadaveric

Outcomes

11 had primary or delayed graft function

7 grafts failed (before death), 2 patients died with working grafts

Longest surviving graft 8 years

12 grafts currently functioning with follow-up times from 24 months to 12 years
2 patients on exchange transfusion pre and post transplantation have good graft function at 6 and 7 years

3 patients have commenced exchange transfusion for poor graft function post transplantation and all have stabilized

2 patients given ALG or ATG have died of sepsis

Recurrent sickling crises post-op is common in patients not receiving exchange transfusion

**Major complications following transplantation:**
1. Delayed graft function
2. Sepsis
3. Recurrent sickle crises
4. Recurrent sickle cell nephropathy
5. There is a risk that repeated transfusion will sensitize patients with HLA antibodies increasing the risk of rejection.
Conclusion

• Sickle cell nephropathy is a relatively common and significant complication of sickle cell disease. Although most patients don’t progress to end-stage renal failure, this complication is becoming more common.

• Moderate to severe renal impairment is associated with a markedly increased risk of mortality

• Patients should be monitored regularly for proteinuria and declining renal function and treated with ACE inhibitors if proteinuria develops. Other causes of chronic kidney disease should be considered and managed.

• HC or regular exchange transfusion may be beneficial in stabilizing deteriorating renal function

• Early transplantation should be considered in patients with severe renal impairment but patient optimization with regular exchange transfusion should be considered both pre and post op.
Thank you