Interplay between iron and inflammatory processes

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Disclosure of Interests

Nothing to declare except participation in several clinical trials of anti-anemic drugs.
My topics

- Inflammation, ESA resistance and functional iron deficiency
- Iron markers
  - Predictors of response to iron?
  - Correlation to inflammation
- Hepcidin and inflammation in CKD
- Associations with mortality in CKD patients
- Treatment with iron
CRP Variation in Hemodialysis Patients Over Three Months

the MIMICK study

CRP are higher in HD patients with comorbidity

p-value <0.01 all weeks except no 3

Anemia in *epoetin-treated* dialysis patients

Greenwood et al, 2003
Functional Iron Deficiency Was Described Early in Epoetin-treated CKD5D Patients

- Combined Phase I and II trial data for recombinant human erythropoietin (rHuEPO) in 25 HD patients with anemia
- rHuEPO administration induced a fall in TSAT and serum iron levels

‘One of the clinical features seen with this form of treatment was a state of functional iron deficiency’

Estimated annual loss of iron in hemodialysis patients

NECOSAD study

- inadequate EPO response in 3.6% of the pts:
  - (1) hemoglobin less than 9.7g/dL,
  - (2) serum ferritin greater than or equal to 200 g/L, and
  - (3) EPO dose greater than or equal to 14,000 IU/week.

Table 2. Possible causes\(^a\) for inadequate erythropoietin (EPO) response of selected patients\(^b\) (N = 57) /1677, 3.6%

<table>
<thead>
<tr>
<th>Causes for inadequate EPO response</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/inflammation</td>
<td>41</td>
</tr>
<tr>
<td>Blood loss</td>
<td>16</td>
</tr>
<tr>
<td>Hyperparathyroidism/aluminum toxicity</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>2</td>
</tr>
<tr>
<td>Folate/vitamin B(_{12}) deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma/myelofibrosis/myelodysplastic syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>5</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate dialysis</td>
<td>2</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
</tr>
<tr>
<td>Graft/shunt problems</td>
<td>14</td>
</tr>
<tr>
<td>Operation</td>
<td>8</td>
</tr>
<tr>
<td>Suspected noncompliance</td>
<td>9</td>
</tr>
<tr>
<td>Medication ((\geq)bone marrow suppress)</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted according to the categorization of the National Kidney Foundation Dialysis Outcome and Quality Investigation (2002).

\(^b\)Some patients fall in more than one category (i.e., there is more than one possible cause for their inadequate EPO response).
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• Inflammation, ESA resistance and functional iron deficiency

• Iron markers
  – Predictors of response to iron?
  – Correlation to inflammation

• Hepcidin and inflammation in CKD
• Associations with mortality in CKD patients
• Treatment with iron
Poor prediction of ESA response by iron markers

Ferritin iron content (%) in CKD 2-5 patients (green) and dialysis patients (blue).

\[ y = 485.89x^{-0.6905} \]

\[ R^2 = 0.3538 \]

Beshara S, unpublished
Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease

- ...all currently available laboratory biomarkers of iron status (either newer or classical markers) do not have an ideal predictive ability when used singly to determine iron deficiency as defined by a response to iron challenge test.
- ...there is insufficient evidence to determine the test performance of the combinations of newer biomarkers, or combinations of newer and classical biomarkers, for diagnosing iron deficiency.
- ...it may be that CHr and %HYPO have better predictive ability for a response to IV iron treatment than classical markers (TSAT <20 or ferritin <100 ng/mL) in HD CKD patients.

Chung M, et al. Comparative Effectiveness Review No. 83. Prepared by the Tufts Evidence-based Practice Center
Hemoglobin Groups and Hypochromic Red Cells
the MIMICK study (unpublished)

Group 1: All Hb>11.0 g/dL
Group 2: At least one Hb≤11.0 g/dL

P<0.001 (between groups)
Relationship hypochromic RBC – ESA resistance in HD patients

\[ y = 0.142x + 0.9635 \]

\[ R^2 = 0.22095 \]
Relationship hypochromic RBC – CRP in HD patients

\[ y = 3.8799x + 8.3077 \]

\[ R^2 = 0.1644 \]
Association between two inflammatory markers (CRP, IL-6) and epoetin resistance in 754 hemodialysis patients.

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Systemic Inflammation – Effects on Erythropoiesis

- Decreased endogenous erythropoietin production
- Suppression of erythropoiesis
  - decreased erythropoietin sensitivity
- Shortened erythrocyte survival
- Impaired iron utilization
Hypoxia and inflammation interplay: coordinates EPO synthesis with iron metabolism.

Modified from Haase V H Am J Physiol Renal Physiol 2010;299:F1-F13
Regulation of hepcidin synthesis.

1. Iron Deficiency
   - TSAT ↓
   - TMPRSS6 Activity ↑
   - HJV ↓
   - BMP6 ↓

2. Increased Erythropoiesis
   - GDF-15 ↑
   - TWSSG1 ↑
   - ? SMAD ↓

3. Hypoxia
   - HIF ↑

4. Inflammation
   - STAT ↑
   - IL-6 ↑
   - IL-1 ↑

Hepcidin levels in CKD patients

Serum hepcidin-25 levels in healthy controls and chronic kidney disease (CKD) patients

Tsuchiya and Nitta. *Therapeutic Apheresis and Dialysis* Volume 17, Issue 1, pages 1-8,
Pre and post erythropoietin (N=7)

Hepcidin (ng/ml)

Pre | 2–4 days | 2–4 weeks
--- | --- | ---
70 | 60 | 60
60 | 50 | 50
50 | 40 | 40
40 | 30 | 30
30 | 20 | 20
20 | 10 | 10
10 | 0 | 0

Ferritin (ng/ml)

* indicates a statistically significant difference.
Anemia and inflammatory variables according to hepcidin tertile groups

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hep, ng/ml</td>
<td>38 (22-61)</td>
<td>110 (96-129)</td>
<td>221 (170-267)</td>
<td></td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.9 (10.9-12.7)</td>
<td>11.8 (11.0-12.7)</td>
<td>12.0 (11.3-12.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Ferritin, g/L</td>
<td>216 (120-380)</td>
<td>422 (296-610)</td>
<td>630 (427-834)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypochromic RBC, %</td>
<td>1.6 (0.75-4.1)</td>
<td>1.1 (0.5-2.7)</td>
<td>1.3 (0.8-4.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>6.4 (2-18)</td>
<td>6.3 (2.6-19)</td>
<td>7.4 (3.0-24.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>8.7 (4.7-14.5)</td>
<td>8.8 (5.5-25.7)</td>
<td>8.2 (5.5-47.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>ESA, IU/kg per week</td>
<td>168(106-240)</td>
<td>119, (71-265)</td>
<td>121 (78-209)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

MIMICK study, ASN poster 2011
Relationship p-hepcidin – IL-6 in hemodialysis patients
Relationship p-hepcidin – p-ferritin in hemodialysis patients

Spearman’s rho=0.58, p<0.001
Molecular regulation of hepcidin by iron and inflammation.

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KDIGO
All-cause mortality associated with transferrin saturation (TSAT) ratio in patients with moderate and advanced non–dialysis-dependent chronic kidney disease.

Association between serum ferritin and all-cause (top) and cardiovascular (CV; bottom) mortality.

Kalantar-Zadeh K et al. JASN 2005;16:3070-3080
Association between administered intravenous iron and all-cause (top) and CV (bottom) mortality.

Kalantar-Zadeh K et al. JASN 2005;16:3070-3080
Table 3. Results of weighted multivariable model for the probability of mortality as a function of iron administered during the prior 6 mo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>None</td>
<td>Ref.</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>&gt; 0 to 700</td>
<td>1.04 (0.91–1.19)</td>
<td>1.04 (0.91–1.19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 700 to 1000</td>
<td>1.00 (0.87–1.14)</td>
<td>1.00 (0.87–1.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 1000 to 1800</td>
<td>0.96 (0.84–1.09)</td>
<td>0.96 (0.84–1.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 1800</td>
<td>1.04 (0.90–1.21)</td>
<td>1.04 (0.90–1.21)</td>
<td></td>
</tr>
</tbody>
</table>

Epoetin Responsiveness Predicts Survival in the Normal Hematocrit Study. Association between epoetin response quartile, and all-cause 1-yr mortality assessed using a Cox proportional hazard model.

Kilpatrick R D et al. CJASN 2008;3:1077-1083
My topics

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• Treatment with iron
Oral iron is often not effective in CKD

Poor absorption
- Inflammation – high hepcidin
- Interaction with other drugs

- Intolerance
- GI-symptoms
Treatment schedules IV iron

- Intermittent (triggered by threshold levels of ferritin and/or TSAT)
  1. Low dose – 10 doses of 100 mg during 3-4 weeks
  2. High dose - 500-1000 mg total dose infusion

- Continuous (depending on response)
  1. Low dose – 10-200 mg*1-3 per 7-28 days
  2. High dose - 1000 mg every third month
Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in patients with chronic kidney disease (CKD) not on dialysis therapy.

The IV iron arm included 421 patients and the oral iron arm included 281 patients.

Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in dialysis patients.

The IV iron arm included 215 patients and the oral iron arm included 205 patients. Serum Hb may be converted from g/dL to g/L by multiplying by 10.

Erythropoiesis-stimulating agent (ESA) dose or change from baseline at end of study for trials comparing intravenous (IV) iron versus oral iron in dialysis patients.

The IV iron arm included 152 patients and the oral iron arm included 156 patients. Abbreviation: CI, confidence interval.

Epoetin dose and Hb throughout DRIVE-II.

Kapoian T et al. JASN 2008;19:372-379

Change from end of DRIVE to end of DRIVE-II p = 0.432

KDOQI
Serum ferritin at baseline, end of DRIVE (wk 6), and end of DRIVE-II (wk 12).

Change from end of DRIVE to end of DRIVE-II p = 0.459

Change from end of DRIVE to end of DRIVE-II p = 0.193

Kapoian T et al. JASN 2008;19:372-379
• 16 ESRD patients with EPO-resistant anemia treated with pentoxifylline for 4 months.
• Baseline *ex vivo* T cell expression of IFN-γ and TNF-α decreased.
Cochrane review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Records identified through database searching: 517
(MEDLINE; EMBASE; CENTRAL; Renal Group's specialised register)

Records identified from other sources: 16

Reports identified: 533

Duplicates removed: 12

Records screened: 521

Records excluded: 428 (title and abstract review)

Excluded studies: 68 (93 reports)
Study participants did not have ESA resistance (57); not RCT (6); wrong population (3); ESA not used in control arm (1); ESA not used (1)

Full text reports assessed: 99

Studies included: 2 (4 reports)

Ongoing studies: 2

Badve et al. Cochrane Database Syst Rev. 2013 Aug
### Interventions for erythropoietin-resistant anaemia in dialysis patients

#### Comparison: 3 ESA and IV iron doses

#### Outcome: 1 EPO dose

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C N</th>
<th>Control N</th>
<th>Mean(±SD)[IU/kg/wk]</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attallah 2006</td>
<td>20 429 (24.7)</td>
<td>21 447 (32.5)</td>
<td></td>
<td>-18.00 [-35.62, -0.38]</td>
<td></td>
</tr>
</tbody>
</table>

#### Comparison: 2 Haematology and biochemistry results

#### Outcome: 1 Haemoglobin

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment N</th>
<th>Control N</th>
<th>Mean(±SD)[g/dL]</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Vitamin C versus control Attallah 2006</td>
<td>20 10.5 (0.9)</td>
<td>21 9.6 (0.8)</td>
<td></td>
<td>0.90 [0.38, 1.42]</td>
<td></td>
</tr>
<tr>
<td>2 High-flux versus low-flux dialyser Ayli 2004</td>
<td>24 11.4 (0.5)</td>
<td>24 9.5 (0.4)</td>
<td></td>
<td>1.90 [1.64, 2.16]</td>
<td></td>
</tr>
</tbody>
</table>

#### Comparison: 3 ESA and IV iron doses

#### Outcome: 2 IV Iron

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C N</th>
<th>Control N</th>
<th>Mean(±SD)[mg/wk]</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attallah 2006</td>
<td>20 26.6 (25.4)</td>
<td>21 26.8 (26.7)</td>
<td></td>
<td>-0.20 [-16.15, 15.75]</td>
<td></td>
</tr>
</tbody>
</table>
Summary

- Inflammation is highly prevalent with large inter- and intraindividual variation in CKD patients.
- Inflammation has several effects on erythropoiesis and is one important regulator of hepcidin.
- Inflammation, functional iron deficiency and ESA hyporesponsiveness are linked to comorbidity and mortality.
- None of the currently available laboratory biomarkers of iron status is a reliable predictor for iron response in CKD patients.
- CKD patients have high hepcidin levels which contribute to anemia, functional iron deficiency as well as ESA and oral iron hyporesponsiveness.
- The optimal treatment of anemia in CKD patients with inflammatory-induced functional iron deficiency and hyporesponse is not established. Long-term safety of different treatment schedules have not been adequately evaluated in clinical trials.
thank you!