IRON & CHRONIC KIDNEY DISEASE

Nilang Patel, MD
Overview

• Prevalence of Iron deficiency anemia

• Iron absorption and it’s metabolism

• How iron metabolism is affected by CKD

• How do you Define or Measure Iron deficiency

• Problems with Iron Indices in CKD patients

• How do you treat – Oral vs. IV formula

• Concerns of iv Iron – Infection / Iron Overload
Prevalence of Anemia in CKD patients

The percentage of patients with either serum ferritin < 100 ng/ml or TSAT < 20% at different levels of CrCl for the combined NHANES cohorts.
**Panel 1: Symptoms of iron deficiency anaemia**

**Very frequent**
- Paleness (45–50%)
- Fatigue (44%)
- Dyspnoea
- Headache (63%)

**Frequent**
- Diffuse and moderate alopecia (30%)
- Atrophic glossitis (27%)
- Restless legs syndrome (24%)
- Dry and rough skin
- Dry and damaged hair
- Cardiac murmur (10%)
- Tachycardia (9%)
- Neurocognitive dysfunction
- Angina pectoris
- Vertigo

**Rare**
- Haemodynamic instability (2%)
- Syncope (0.3%)
- Koilonychia
- Plummer-Vinson syndrome (<0.1%)
Normal Erythropoiesis

Iron dependence

Erythropoietin

Iron

~ 10-13 days

~ 21 days

~ 1-2 days

Pluripotent Stem Cell

Burst-Forming Unit-Erythroid Cells (BFU-E)

Colony-Forming Unit-Erythroid Cells (CFU-E)

Proerythroblasts

Erythroblasts

Reticulocytes

RBCs
Iron

- Iron, fourth most abundant element in earth's crust
- Iron is an essential element for survival, required by all cells
  - Involved in electron transport reactions, oxygen carrying and metabolism
- Concentration is tightly regulated as it can by toxic
  \[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{OH}^- + \text{Fe}^{3+} + \text{OH}^- \]
- Regulation by controlling iron release into the plasma
**Distribution of Iron in Adults**

**Dietary Iron**
- 1-2 mg absorb

**Storage Iron**
- 24 mg
  - Circulating erythrocytes (hemoglobin) (1800 mg)
  - Reticulo-endothelial macrophages (600 mg)
  - Sloughed mucosal cells
  - Desquamation
  - Menstruation
  - Other blood loss
  - 1-2 mg loss

**Used By:**
- Muscle (myoglobin) (300 mg)
- Liver parenchyma (1000 mg)
- Bone marrow (300 mg)

(Recycling Senescent RBC)
Circulating red blood cells

Reticuloendothelial macrophages

Muscle, other parenchymal cells

GI tract

Erythroid marrow

Hepatocytes

Functional iron

Macrophage storage iron

Hepatocyte storage iron

Transport iron

Sites of hepcidin control of iron entry into plasma
Utilized by BM or stored as Ferritin in Liver, Spleen

Attach to TFR1 of cell surface and internalize

Ferroportin channels presents on Reticuloendothelial macrophages and Hepatocytes

Hepcidin

Anemia
ESAs
Dialysis clearance
Hypoxia

Reduced GFR
Iron
Inflammation

IL-6
Lipopolysaccharide

Hepcidin Increased in CKD and Dialysis Patients

Hepcidin Increased in patients with Inflammation
Role of inflammation and hepcidin in anemia of CKD

Sequestration of Iron
Functional Iron deficiency
Causes of Iron Deficiency in CKD Patients

- Increased blood loss
  - phlebotomy,
  - blood trapping in the dialysis apparatus
  - gastrointestinal or other bleeding as a result of uremic platelet

- Increased iron utilization from ESA therapy

- Impaired dietary iron absorption - Antacids and Phosphate binders

- Impaired iron release from body storage sites

- Hepcidin excess also contributes to the impaired dietary iron absorption
  and impaired iron release from body storage sites. (Functional Iron Deficiency)
How do you measure Iron Deficiency?

• **Gold Standard** is Bone marrow biopsy looking Iron Store.

• **Practice Sense**: Whether patient respond to Iron therapy or not?

• Poor bone marrow iron store – Not accurately predict response to Iron therapy in most patient.

• Adequate bone marrow iron store - still shows response of by Iron therapy.
-100 nondialysis CKD patient with Anemia on ESA therapy and Iron naïve.
-Bone marrow iron stores were evaluated by aspiration. Hgb, TSAT, Ferritin were measured at baseline and 1 month after 1000 mg of intravenous iron sucrose.
- Posttest predictive values for the erythropoietic response (> or =1-g/dl increase in hemoglobin) calculated

*Figure 2. Percentages of positive peripheral or bone marrow iron tests, according to the response to 1000 mg of intravenous iron (≥1-g/dl increase in Hb) in 100 nondialysis patients with CKD. sFerr, serum ferritin. *P < 0.05.*
• The sensitivity and the specificity of central and peripheral iron indices to identify the erythropoietic response was similar and moderate.

• Areas under the ROCs were approximately 70% and did not differ from one test to another.

Figure 3. Sensitivity and specificity of TSAT and serum ferritin (ferritin) and their combination (TSAT + ferritin) and bone marrow iron (BM iron) to identify correctly a positive erythropoietic response (≥1-g/dL increase in Hb [ΔHb]) to intravenous iron in 100 nondialysis patients with CKD (areas under the ROCs). The areas under the ROCs do not differ in the case of TSAT, ferritin, and BM iron, but TSAT + ferritin area under the ROC is significantly lower than the other. *P < 0.05 versus TSAT and ferritin.

Neither serum ferritin nor transferrin saturation were completely adequate diagnostic tools.
Serum ferritin levels less than 200 ng/dL were 100% specific for the diagnosis True IDA but only 41% sensitive.
Transferrin saturation of less than 20% was 88% sensitive, but only 53% specific.
Overall..

- Sensitivity of TSAT < 20% is low (60-80%)

- Sensitivity of Ferritin < 100 ng/ml ~ 35-48%
  < 200 ng/ml ~ 40%

- Only half of patient who respond to additional IV iron therapy have a Ferritin < 100 and TSAT < 20%
Problem with Ferritin

• Ferritin is a positive acute phase reactant.

• Ferritin – has sex differences (15% variability in Male, 30% in Female)
  - interpersonal variability
    (ranged 2–62% measured over an initial two-week period )
  - variability based on Assay (~ upto 150 ng/ml)

    (Kidney Int. 2009 Jan;75(1):104)

• Transferrin - is negative acute phase reactant
  - affected by protein-energy wasting / Diurnal variation
### Table 1. Effect of Test Accuracy and Prevalence of Iron Deficiency on Iron Use

<table>
<thead>
<tr>
<th>Marker</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin &lt; 200 ng/mL</td>
<td>44%</td>
<td>77%</td>
<td>38%</td>
<td>49%</td>
<td>68%</td>
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<tr>
<td>20%</td>
<td>20%</td>
<td>77%</td>
<td>38%</td>
<td>24%</td>
<td>87%</td>
</tr>
<tr>
<td>TSAT &lt; 20%</td>
<td>44%</td>
<td>61%</td>
<td>79%</td>
<td>70%</td>
<td>72%</td>
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<td>20%</td>
<td>20%</td>
<td>61%</td>
<td>79%</td>
<td>42%</td>
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</tr>
<tr>
<td>TSAT &lt; 20% and serum ferritin &lt; 100 ng/mL</td>
<td>44%</td>
<td>33%</td>
<td>98%</td>
<td>93%</td>
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<tr>
<td>20%</td>
<td>20%</td>
<td>33%</td>
<td>98%</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>%HRC &gt; 6%</td>
<td>44%</td>
<td>82%</td>
<td>95%</td>
<td>93%</td>
<td>87%</td>
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<tr>
<td>20%</td>
<td>20%</td>
<td>82%</td>
<td>95%</td>
<td>80%</td>
<td>95%</td>
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<tr>
<td>CHr &lt; 29 pg</td>
<td>44%</td>
<td>57%</td>
<td>93%</td>
<td>86%</td>
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<tr>
<td>20%</td>
<td>20%</td>
<td>57%</td>
<td>93%</td>
<td>67%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Abbreviations: %HRC, percentage of hypochromic red blood cells; CHr, reticulocyte hemoglobin content; NPV, negative predictive value; PPV, positive predictive value; TSAT, transferrin saturation.

*The higher prevalence estimates are for a group of patients with CKD stage 4 or 5. A smaller proportion of patients may have been included in the national laborite population monitored.

*Representative data from a small subset of patients with insufficient cohort size to make meaningful statements.

*True positive as a percentage of all positive values; therefore, the percentage of patients with positive test results correctly identified as iron replete or responsive to iron therapy.

*True negative as a percentage of all negative values; therefore, the percentage of patients with negative test results correctly identified as iron replete or unresponsive to iron therapy.

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**Problem:** Blood storage time leads artificial RBC expansion, so not useful for dialysis centers who is using national laborites.
**KDIGO 2012 : IRON THERAPY**

- Trial of IV iron (or in CKD non-dialysis (ND) patients alternatively a 1–3-month trial of oral iron therapy) if (2C):
  - an increase in Hgb concentration without starting ESA treatment is desired and
  - TSAT is ≤30% and ferritin is ≤500 ng/ml
  - Reduction in ESA dose is desired

- **IV iron should not routinely be administered in patients with serum ferritin levels that are consistently >500 ng/ml.**
A randomized trial of intravenous and oral iron in chronic kidney disease

Rajiv Agarwal¹, John W. Kusek² and Maria K. Pappas¹

- Randomized 136 pt with CKD stage 3-4 (GFR 20-60 ml/min/1.73m²) and IDA (Hgb < 12 + Ferritin < 100 or TSAT < 25%)
- Open Label, Single Center
- Oral ferrous sulfate (325 mg TID for 8 weeks) or IV Iron Sucrose (200mg q 2w, total 1 g)
- Higher Cardiovascular and Infectious S/E in IV iron group
FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall¹, Andreas H. Bock², Fernando Carrera³, Kai-Uwe Eckardt⁴, Carlo Gaillard⁵,

-56-week, open-label, multicenter, prospective and randomized study of 626 patients with nondialysis-dependent CKD, anemia and iron deficiency not receiving ESAs.

-Randomized (1:1:2) to IV ferric carboxymaltose (FCM), targeting a higher (400–600 μg/L) or lower (100–200 μg/L) ferritin or oral iron therapy.

-The primary end point was time to initiation of other anemia management (ESA, other iron therapy or blood transfusion) or hemoglobin (Hb) trigger of two consecutive values <10 g/dL during Weeks 8–52.
FIGURE 2: (A) Time to initiation of other anaemia management or Hb trigger (Kaplan–Meier estimates) and LS mean locally measured observed values over time for (B) Hb (C) ferritin and (D) TSAT according to treatment group (ITT population). Measurements of Hb, ferritin and TSAT were included up to the point at which other anaemia therapy was initiated (with or without cessation of randomized study drug) and/or the patient discontinued the study. BL, baseline; FCM, ferric carboxymaltose.
• Rate of Adverse Events were similar in all groups.

• Non-adherence was 16.4% in the oral iron treatment group.
IV Iron vs. Oral Iron in Dialysis Patients

IV Iron improves Hgb better than Oral iron

KADIGO Says “IV iron should not routinely be administered in patients with serum ferritin levels that are consistently >500 ng/ml”.

Is there any data for response to IV Iron therapy Ferritin > 500 ng/ml?

IV iron decrease ESAs dose better than Oral iron

DRIVE STUDY I and II (observation)

A Schematic of the Study Procedures of DRIVE and DRIVE-II

- Major inclusion criteria: Hb ≤ 11 g/dL, TSAT ≤ 25%, Ferritin 500-1200 ng/mL, Epoetin dose ≥ 22,500 IU/week, and ≤ 125 mg/week IV iron in any of the 4 weeks preceding enrollment
- Major exclusion criteria: active infection, recent blood loss, recent inpatient hospitalization

Coyne DW et al, J Am Soc Nephrol. 2007 Mar;18(3):975-84
DRIVE Trial: Use of Ferritin to Guide IV Iron Use

- 47% responded to IV iron with >2 g/dL increase in Hgb
- Ferritin of 500 to 1200 ng/mL had no predictive value
- Withholding IV iron leads to iron-restricted erythropoiesis as seen by steadily falling reticulocyte Hgb content 9CHr)

Coyne DW et al, J Am Soc Nephrol. 2007 Mar;18(3):975-84
IV Iron (solid line)
control (dashed line)
Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski1,2*, Dirk J. van Veldhuisen3, Josep Comin-Colet4, Georg Ertl5,6,

• Multi-center, double-blind, placebo-controlled trial that enrolled 304 ambulatory symptomatic HF patients with LVEF ≤45%, elevated natriuretic peptides, and iron deficiency (ferritin < 100 ng/mL or 100–300 ng/mL if TSAT < 20%).

• Patients were randomized 1 : 1 to treatment with i.v. iron, as ferric carboxymaltose (FCM, n= 152) or placebo (saline, n= 152) for 52 weeks
Improve HF symptoms, NYHA class, 6MWT, Fatigue score, QoL score.

Decrease Hospitalization for HF

Figure 4 Time to first hospitalization due to worsening heart failure. The time to first hospitalization due to worsening heart failure was estimated using the Kaplan–Meier method, on the full-analysis set. Subjects were censored at their death, study completion, or withdrawal date.
- Based on this and other observational Studies which showed improvement in Hgb after trial of IV iron even with patient with high ferritin level

+ Change in reimbursement of dialysis treatment

+ Concern of adverse effects of ESAs

- IV iron usage increased in across the all dialysis units in US.
The DOPPS Practice Monitor for US Dialysis Care: Update on Trends in Anemia Management 2 Years Into the Bundle

- Nearly 40% of US dialysis patients have Ferritin > 800 ng/ml

- 40% of US dialysis patients have Ferritin > 800 ng/ml
• It is clear that raising Ferritin and TSAT with IV Iron reduces ESA doses and lower costs and it is possible that increasing Hgb levels with more IVI and fewer ESAs may improve outcome?

• Should we need to concern about Iron Overload or other adverse effect of IV iron therapy?
Hemodialysis-associated Hemosiderosis in the Era of Erythropoiesis-stimulating Agents: A MRI Study

Guy Rostoker, MD, PhD, a Mireille Griuncelli, MLT, a Christelle Loridon, MLT, a Renaud Couprie, MD, b

- Measured Liver iron concentration by means of T1 and T2* contrast MRI without gadolinium, in a cohort of 119 fit hemodialysis patients receiving both parenteral iron and ESA, in keeping with current guidelines.

- Excluded patient with overt inflammatory or infectious disease or malnutrition.

- Most of the patients are with relatively low Comorbidities index
Only 19 of the 119 hemodialysis patients (16%) had normal hepatic iron stores (≤50 μmol/g), whereas the remaining 100 patients had mild to severe hepatic iron overload (84%).

-25 (21%) Pt has Ferritin < 100 g/L
-22 (19%) Pt has Ferritin 100-200 g/L
-22 (19%) Pt has Ferritin > 500 g/L
-6 (5%) Pt has Ferritin > 800 g/L

Figure 1  Time course of hepatic iron stores studied by magnetic resonance imaging in hemodialysis patients. (A) Initial and final hepatic iron concentrations at magnetic resonance imaging (MRI) in 11 patients during iron therapy. (B) Initial and final hepatic iron concentrations at MRI in 33 patients with hepatic iron overload after iron withdrawal (n = 19) or a major iron dose reduction (n = 14).
The odds ratio for hepatic iron overload on MRI was 3.9 (95% CI: 1.81 to 8.4) with >250 mg/month of IV iron as compared to <250 mg/month.

Figure 1.a: Histogram of Iron per month

Rostoker et al, PLOS ONE; DOI:10.1371 December 15, 2014
Kinetics and efficacy of deferoxamine in iron-overloaded hemodialysis patients

John Stivelman, Gerald Schulman, Martin Fosburg, J. Michael Lazarus, and Raymond M. Hakim

Most of the Hemochromatosis patient has Invariable high TSAT > 80% (definitely > 50%)

### Table 1. Patient characteristics: Acute study

<table>
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<th>Sex</th>
<th>Age</th>
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<th>DT</th>
<th>Hct</th>
<th>Nx</th>
<th>Ferr</th>
<th>% Sat</th>
<th>Tx</th>
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<td>1965</td>
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</tr>
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</table>

6/6  | 35  | 53.3| 117| 23.3|     | 8,168| 88.3  | 238 | 56.1| 96.8| 501 | 831   |

±2.6 | ±3.4| ±15 | ±1.1|     | ±1,265| ±4.9 | ±46 | ±8.4| ±25.4| ±155| ±157  |

Abbreviations are: Wt, weight (kg); DT, time on dialysis (months); Nx, nephrectomy; Ferr, ferritin concentration (ng/ml); % Sat, % saturation of total iron binding capacity; Tx, number of units of RBC transfusions; OT, serum glutamic oxaloacetic transaminase (IU) (N = 4–40 IU); PT, serum glutamic pyruvic transaminase (IU) (N = 6–55 IU); Alk, alkaline phosphatase (IU) (N = 40–110 IU); Fe/wt, iron burden in mg/kg body weight.
IV iron and Outcome

- Treatment indication Bias
- Sicker patients more need of IV iron
- Lead time Bias (Prevalent patient)
- Mostly higher Comorbidities burden driving Functional Iron Deficiency – more IV iron

Outcome observation started 1 month after the 4-month IV iron dose ascertainment period (5 months after study enrolment) and ended at the time of death.

- The median (interquartile range) follow-up time for mortality analyses was 1.7 (1.0–2.4) years.

• 14,078 Incident dialysis patients between 2003 and 2008.
• IV iron dose accumulations over 1-, 3-, and 6-month exposure.
• Marginal structural modeling to control for time-dependent confounder
• No difference in all-cause, cardiovascular or Infection related mortality

IV iron and Outcome

- So, observational Cohort studies have conflicting results.
- May be affected by Publication bias too.

- Prospective RCTs looking between IV iron vs Oral Iron up to 1 year duration did not see difference in mortality.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hospitalizations and deaths (full-analysis set)</th>
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<tr>
<td>End-point or event</td>
<td>FCM (n = 150)</td>
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<tr>
<td></td>
<td>Total number of events</td>
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<tr>
<td>Death</td>
<td>12</td>
</tr>
<tr>
<td>Death for any cardiovascular reason</td>
<td>11</td>
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<tr>
<td>Death due to worsening HF</td>
<td>4</td>
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<tr>
<td>Death due to other cardiovascular reason</td>
<td>7</td>
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</tbody>
</table>

- Similarly FIND-CKD trial also did not see any difference
- Although, they are not designed to look this differences

Iron and Infection

In Vivo and Vitro Study shows that Iron can:

- increase bacterial growth
- impair neutrophil and T-cell function
- impaired host immunity
Iron and Infection

Table 3. Results of Cox regression analyses of the risk of bacteremia in patients undergoing hemodialysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Iron replete(^a)</td>
<td>2.3 (1.0–5.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Diabetes mellitus(^b)</td>
<td>2.6 (1.2–5.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Venous catheter use(^c)</td>
<td>5.5 (2.4–12.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^a\) Compared with patients who were not iron replete.
\(^b\) Compared with patients who did not have diabetes mellitus.
\(^c\) Compared with patients who were not using a venous catheter.

132 HD patients observed for 1 year after receiving IV iron for bacteremia.

Iron replete (TSAT > 20% or Ferritin > 100ng/ml)
Risk of infection in patients who received intravenous iron.

Edward Litton et al. BMJ 2013;347:bmj.f4822
Iron and Infection

- IV Iron Loading Dose > Maintenance dose
- Prospective RCTs looking between IV iron vs Oral Iron up to 1 year duration did not see difference.

- No clear evidence of increase risk of Infection in Hemochromatosis

**KDIGO: IRON DURING INFECTION**

- “Current evidence cannot provide a Clear Answer”

- Caution Advised: “Clinical judgment is necessary in each individual patient to assess whether there is an immediate need for IV iron (as opposed to delaying treatment until resolution of an infection).
Iron and Oxidative stress

• Free iron is a potent oxidizing agent leads to formation of free oxygen radicals.

• Reactive oxygen species leads to endothelial dysfunction and atherogenesis.
Correlation between iron dose and CCA-IMT in patients younger than 60 years.

- Cohort of 79 pt. on HD.

- Measurements of common carotid artery intima-media thickness (CCA-IMT) assessed by B-mode USG.

- Correlated with the intravenous iron dose received during the 12 months preceding the study.
Summary

• Ferritin level has lots of issue in guiding treatment.

• Trial of Oral Iron should be given to CKD pt.

• There is concern for IV iron and increase risk of Iron overload, Infection and mortality but data are not strong and mostly derived from Cohort.
Thank you !!
The Proper Use of Ferritin to Guide Decisions on IV Iron Use

CKD 3 and 4

1. A low ferritin (<100 ng/mL) usually indicates low iron stores.
2. A higher ferritin lacks predictive value. Use clinical judgment on whether to give IV or oral iron.
3. IV iron can raise Hgb, delay or prevent the need for ESA therapy, or lower ESA doses.

Patients on Dialysis

1. A low ferritin (< 200 ng/mL) usually indicates low iron stores.
2. A higher ferritin lacks predictive value. Use clinical judgment on whether to give IV iron.
3. IV iron can raise Hgb and lower ESA doses and cost.
Table 4. Area under the receiver operating characteristics (ROC) curve of iron biomarkers for diagnosis of iron overload (LIC > 50 micromol/g) in 212 hemodialysis patients studied by hepatic MRI.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Overall Cohort (n°1 + n°2)(n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (micromol/L)</td>
<td>0.556 [0.466 to 0.645] p = 0.223</td>
</tr>
<tr>
<td>Serum Transferrin (g/L)</td>
<td>0.703 [0.623 to 0.783] p &lt; 0.0001</td>
</tr>
<tr>
<td>Serum Ferritin (microg/L)</td>
<td>0.767 [0.698 to 0.835] p &lt; 0.0001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>0.634 [0.552 to 0.715] p = 0.001</td>
</tr>
<tr>
<td>Serum soluble transferrin receptor (sTfR) (mg/L)</td>
<td>0.545 [0.455 to 0.636] p = 0.327</td>
</tr>
<tr>
<td>sTfR/Ferritin ratio</td>
<td>0.709 [0.629 to 0.789] p &lt; 0.0001</td>
</tr>
<tr>
<td>Serum Hepcidin (ng/mL)</td>
<td>0.710 [0.631 to 0.789] p &lt; 0.0001</td>
</tr>
<tr>
<td>Erythrocyte mean corpuscular Volume (fL)</td>
<td>0.556 [0.464 to 0.648] p = 0.233</td>
</tr>
</tbody>
</table>

Data are given as area of the ROC curve with the [95% confidence interval].
<table>
<thead>
<tr>
<th>Variables</th>
<th>Positive Control Group (n = 9)</th>
<th>Normal (≤50 μmol/g) (n = 19)</th>
<th>Mild Overload (51-100 μmol/g) (n = 42)</th>
<th>Moderate Overload (101-200 μmol/g) (n = 22)</th>
<th>Severe Overload (&gt;201 μmol/g) (n = 36)</th>
<th>P Value Kruskal-Wallis Test or ( \chi^2 ) Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 (38-77)</td>
<td>72 (29-81)</td>
<td>60 (21-87)</td>
<td>50.5 (19-79)</td>
<td>62 (25-84)</td>
<td>.10 at Kruskal-Wallis (&lt;.05 at ( \chi^2 ))</td>
</tr>
<tr>
<td>Female sex, n patients (%)</td>
<td>4/9 (44.44%)</td>
<td>3/19 (15.79%)</td>
<td>20/42 (47.62%)</td>
<td>12/22 (54.54%)</td>
<td>11/36 (30.55%)</td>
<td>0.24 at Kruskal-Wallis (.66 at ( \chi^2 ))</td>
</tr>
<tr>
<td>Dialysis vintage before MRI (months)</td>
<td>ND (3-68)</td>
<td>13.5 (2-93)</td>
<td>9.5 (2-85)</td>
<td>23 (2-95)</td>
<td>35/36 (97.320%)</td>
<td>(&lt;.05 at Kruskal-Wallis P = .03 )</td>
</tr>
<tr>
<td>ESA therapy, n patients</td>
<td>ND</td>
<td>42/42 (100%)</td>
<td>22/22 (100%)</td>
<td>36/36 (100%)</td>
<td>36/36 (100%)</td>
<td>(&lt;.01 at ( \chi^2 ))</td>
</tr>
<tr>
<td>Darbepoetin dose (μg/month)</td>
<td>ND</td>
<td>132.50 (31.20-471.60)</td>
<td>194 (23.30-566)</td>
<td>122.30 (0-430)</td>
<td>172.10 (39.50-900)</td>
<td>(&lt;.0001 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Parenteral iron therapy, n patients (%)</td>
<td>ND (78.95%)</td>
<td>40/42 (95.24%)</td>
<td>22/22 (100%)</td>
<td>36/36 (100%)</td>
<td>172.10 (39.50-900)</td>
<td>(&lt;.0001 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Iron dose (mg/month)</td>
<td>ND</td>
<td>150.30 (0-700)</td>
<td>282.90 (128.60-500)</td>
<td>172.10 (39.50-900)</td>
<td>250 (210-340)</td>
<td>(&lt;.0001 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Hepatic iron content at MRI (μmol/g dry weight)</td>
<td>210 (70-280)</td>
<td>70 (55-100)</td>
<td>180 (120-200)</td>
<td>250 (210-340)</td>
<td>172.10 (39.50-900)</td>
<td>(&lt;.0001 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Dialysis comorbidity index</td>
<td>ND</td>
<td>4 (0-13)</td>
<td>3 (0-12)</td>
<td>3 (0-6)</td>
<td>3 (0-11)</td>
<td>.44 at Kruskal-Wallis &lt;.01 at ( \chi^2 ))</td>
</tr>
<tr>
<td>Diabetes, n patients (%)</td>
<td>1/9 (11.11%)</td>
<td>4/19 (21.05%)</td>
<td>8/42 (19.05%)</td>
<td>5/22 (22.73%)</td>
<td>10/36 (27.78%)</td>
<td>.8526 at ( \chi^2 ) (.41 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Audit score</td>
<td>ND</td>
<td>1 (0-6)</td>
<td>2 (0-10)</td>
<td>2.5 (0-36)</td>
<td>2.5 (0-36)</td>
<td>(.41 at Kruskal-Wallis )</td>
</tr>
<tr>
<td>Hemochromatosis gene, n patients (%)</td>
<td>3/9 (33.33%)</td>
<td>0/19 (0%)</td>
<td>4/42 (9.52%)</td>
<td>1/22 (4.54%)</td>
<td>2/36 (5.55%)</td>
<td>.51 at ( \chi^2 ) &lt;.01 at ( \chi^2 ))</td>
</tr>
</tbody>
</table>

*ESA* = erythropoiesis-stimulating agents; *MRI* = magnetic resonance imaging; *ND* = not done.

Values are given as median and (range).
HIF-2 stimulates renal and hepatic erythropoietin synthesis, which raises serum erythropoietin levels, stimulating erythropoiesis in the bone marrow. In the duodenum, DCYTB reduces Fe\(^{3+}\) to Fe\(^{2+}\), which then enters enterocytes via DMT1. DCYTB and DMT1 are both regulated by HIF-2. Iron is then released into the circulation via FPN, which is also HIF-2-inducible. In the circulation iron is transported in a complex with TF to the liver, bone marrow and other organs; cells of the reticuloendothelial system acquire iron through the phagocytosis of senescent red cells. TF is HIF-regulated, and hypoxia and/or pharmacologic PHD inhibition raises TF serum levels. Increased erythropoietic activity in the bone marrow produces GDF15 and erythroferrone, which suppress hepcidin in hepatocytes. Hepcidin suppression increases FPN expression on enterocytes, hepatocytes and macrophages, resulting in increased iron absorption and mobilization from internal stores. Inflammation stimulates hepcidin production in the liver and leads to reduced FPN expression and hypoferraemia.

In the normal kidney, EPCs are recruited from peritubular interstitial fibroblast-like cells and pericytes. Tubular epithelial cells do not produce EPO. Under conditions of injury, EPCs or interstitial cells with EPC potential transdifferentiate into myofibroblasts, which synthesize collagen and lose their ability to produce EPO. In CKD, EPC recruitment is impaired, resulting in reduced renal EPO output and the development of anaemia. Under conditions of severe hypoxia or in patients with advanced CKD, the liver contributes to plasma EPO levels. Abbreviations: CKD, chronic kidney disease; EPC, erythropoietin-producing cell; EPO, erythropoietin.

Overview of erythropoiesis

Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.82
ALTERNATIVE AND NOVEL DIAGNOSTIC TOOLS FOR IRON AND ANEMIA MANAGEMENT IN CKD

- Reticulocyte hemoglobin content (CHr)
- Percentage of hypochromic RBCs (%HRC)
- Soluble transferrin receptor (sTFR)
- Hepcidin

• Similarly, Ferritin not helpful in finding out iron overload.

<table>
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<th>Mild Overload (51-100 µmol/g) (n = 42)</th>
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<th>Severe Overload (&gt;201 µmol/g) (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>99.33 (27.67-631.30)</td>
<td>205.80 (37-1383)</td>
<td>215.20 (15-949.50)</td>
<td>446.10 (55.25-1299)</td>
</tr>
<tr>
<td>Transferrin saturation (TSAT) (%)</td>
<td>21.33 (7.83-40)</td>
<td>19.25 (7.67-47.70)</td>
<td>24.32 (6.33-41.33)</td>
<td>30.87 (8-72.16)</td>
</tr>
<tr>
<td>Hepcidin (ng/mL)</td>
<td>52.33 (0.76-554.80)</td>
<td>102.80 (6.53-421.40)</td>
<td>87.90 (1.10-250.20)</td>
<td>162.70 (5.29-1036)</td>
</tr>
</tbody>
</table>

119 Hemodialysis pt. included in the Cross-sectional Study (Classified According to Hepatic Nonheme Iron Stores as Measured by Hepatic MRI)

Mechanisms of Anemia in CKD
Hypo-Responsiveness to ESAs

- Iron deficiency
- Inflammation
  - Chronic infections
  - Failed renal allograft
- Hematological disorders or malignancy
- Hyperparathyroidism
- Nutritional—Folate, vitamin B12, carnitine
- Drugs: ACE/ARB, AL++ overload
- Inadequate dialysis/oxidative stress
Estimated Annual Iron Requirement in CKD Patients

Average annual iron losses due to:

- Repeated laboratory tests ~ 0.5 g
- Accidental losses during HD and other bleeding events ~ 1.0 g
- Blood retention in hemodialyzer and tubing ~ 1.0 g
- Normal iron losses ~ 0.5 g

Total annual iron loss ~ 3.0 g

**Figure 2.** Estimated annual loss of iron in each chronic hemodialysis patient.
Figure 2  Correlation between infused iron and iron stores in 11 hemodialysis patients. The Figure shows the relationship between the infused dose of iron per month and the increase in iron stores per month evaluated by magnetic resonance imaging (MRI) in 11 hemodialyzed patients. The relationship was studied by the Spearman correlation test, which showed a very high correlation (rho = 0.854; P = .0015).
ROC Curves of ferritin compared to a combination of the eight biomarkers for predicting iron overload (LIC > 50 μmol/g) in 212 hemodialysis patients studied by quantitative hepatic MRI.

* Combined biomarkers comprising serum iron + ferritin + Transferrin + TSAT+ serum soluble transferrin receptor + STfR/Ferritin ratio + hepcidin + C-reactive protein
Table 6. Area under the receiver operating characteristics (ROC) curve, optimal threshold values and diagnostic accuracy of serum ferritin and the serum soluble transferrin receptor/ferritin ratio to detect severe iron overload (LIC > 200 micromol/g) as determined in 212 hemodialysis patients studied by hepatic MRI.

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort (n = 212 patients) ROC Curve Area</th>
<th>Optimal threshold value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Diagnostic accuracy</th>
<th>Likelihood Ratio for a positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin (microg/L)</td>
<td>0.81 [0.74 to 0.87] p&lt; 0.0001</td>
<td>290.20</td>
<td>72.30 [58.10–83.10]</td>
<td>77 [69.90–82.70]</td>
<td>75.9%</td>
<td>3.14</td>
</tr>
<tr>
<td>sTfR/Ferritin ratio</td>
<td>0.78 [0.70 to 0.87] p&lt; 0.0001</td>
<td>17.21</td>
<td>75 [58.70–86.30]</td>
<td>71 [63.30–77.50]</td>
<td>71.7%</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Values of area of the ROC Curve are given with the [95% confidence interval].
Values of sensitivity and specificity are given with [95% confidence interval].

doi:10.1371/journal.pone.0132006.t006
‘Guidelines are for the population, while the doctor is for the patient!’