Iron Overload in CKD and Effects on Various Tissues

Kamyar Kalantar-Zadeh, MD, MPH, PhD
FACP, FAAP, FAHA, FASN, FNKF
Professor of Medicine, Pediatrics and Public Health
Chief, Division of Nephrology and Hypertension
University of California Irvine, School of Medicine
Harold Simmons Center for Kidney Disease Research & Epidemiology
Professor of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA
President Elect
International Society of Renal Nutrition & Metabolism (ISRN M)
www.RenalNutrition.com
Disclosure of Interests

Alphabetical order:

**Abbott**: Grant, Speaker bureau

**Affymax**: Advisory Board

**Amgen**: Advisory Board, Speaker bureau

**BBraun**: Speaking engagement

**DaVita**: Grant, medical directorship

**Fresenius**: Speaker bureau, Consultant

**Genzyme**: Consultant, proctorship

**Keryx**: Advisory boards

**NKF**: Grants, advisory boards

**NIH**: Study sections, grants

**Otsuka**: Speaker bureau, consultation

**Rockwell**: Advisory board

**Shire**: Speaker bureau, consultation

**Vifor**: consultation
We cope well with iron shortage...

• The human body has many mechanisms to absorb, transfer, and store iron

• Iron Deficiency (ID) is the most common deficiency state in the world
  Most common causes of ID in non-CKD:
  – Blood loss
  – Diet
  Most common causes of ID in CKD:
  – GI blood loss?
  – ESA use without iron?

• Iron Reserves: ~1000 mg of iron is stored as ferritin (1/3 of total body iron)

• Intestinal absorption of iron increases in response to deficiency
But we cope poorly with iron excess

- **Hepcidin system to “trap” iron … but it does not get rid of excess iron**

- Some iron is excreted by shedding of intestinal cells?

- There is no effective physiologic mechanism to “excrete” excessive iron
Spectrum of chronic iron overload

- Transfusional iron overload
- Genetic iron overload
- IV iron in CKD pts?
Blood transfusion can overwhelm the iron balance

- Normal daily iron flux: 1-2 mg
- Each unit of PRBC: 200-250 mg
- IV iron to hemodialysis patients: 50-400 mg

But... ESA therapy in ESRD pts likely has prevented and even cured iron overload, be it from PRBC transfusion or IV iron!
When does iron become a problem?

• Normally 2.5 – 3 grams of iron in the body.

• Tissue damage when total body iron is 7 – 15 grams
  – After 30-50 units of red blood cells (e.g. in Thalassemia)
Correlation between serum ferritin levels and transfusion burden

Kattamis C et al. The Management of Genetic Disorders 1979;351–359
Transfusions Dramatically Decreased in Medicare Patients on Dialysis 1989-2007

1989: Recombinant Human Erythropoietin Introduced

Hb Level and Total Blood Transfusions Over Time

Inpatient and Outpatient Transfusions

Mean Hb (g/dL)

Hemodialysis Patients Transfused per Quarter (%)

RBC Transfusion Rate in increased in dialysis patients since 2010

- An analysis conducted by the CMS found that the average monthly blood transfusion rate increased 19% between 2010 and 2011.¹

USRDS data demonstrated an increase in transfusions between 2011 and 2012.²

USRDS = United States Renal Data System; CMS = Centers for Medicare & Medicaid Services.

*USRDS data are for period prevalent patients on dialysis in 2011 and 2012. Only patients with a dialysis claim during the month were included in the analysis.

USRDS data demonstrated an increase in transfusions in patients on hemodialysis.

Monthly comparisons between 2010 and 2012 showed a 22% to 33% increase in the percent of patients receiving transfusions.

USRDS = United States Renal Data Systems.

*USRDS data are for patients on dialysis with at least one transfusion event during the month.

Iron Overload Effects on Various Tissues

- **Bone System**: Bone loss & deformities, Arthropathy
- **Bone Marrow**: Reticuloendothelial System
- **Liver**: Cirrhosis
- **Cardiovascular System**: Heart failure, AS
- **Endocrine organs**: Diabetes, Hypogonadism
- **Survival & QoL**

**Free Iron (NTBI, LPI?)**
Dangerous iron species

R.O.S
(Reactive Oxygen Species)
Lessons from thalassemia, sickle cell, MDS

- Hepatic fibrosis → Cirrhosis
- Cardiomyopathy
- Hypoparathyroidism
- Hypothyroidism
- Diabetes
- Hypogonadism
- Arrhythmia
Visceral targets of iron overload: liver and heart

Hepatocyte siderosis

Post-mortem cardiac iron deposits correlate with blood transfusions

Units of blood transfused

Patients with cardiac iron (%)
Impact of iron overload on endocrine glands

- Lower height of pituitary gland

- Hypogonadism (50% patients)

- Short stature
Iron overload causes insulin deficiency and insulin resistance and diabetes

- Iron overload causes apoptosis of beta cells which are exquisitely susceptible to oxidative stress due to their limited antioxidant capacity and high affinity for Fe uptake.

- Even subtle increases in dietary iron content (red meat) and modest elevation of body iron pool are associated with insulin resistance, metabolic syndrome, and gestational diabetes.

- Iron deficiency & reduction of body iron pool with bloodletting or blood donation ameliorates insulin resistance and improves glycemic control in type 2 diabetics.

- Iron chelation therapy and blood donation reduce the risk of diabetes in normal subjects.

Vaziri et al, multiple publications
Iron overload & risk of infections

- Infection is the second most common cause of mortality among ESRD patients

- Iron overload → increased susceptibility to infections in both ESRD and general populations.
  - Fe is essential for bacterial multiplication & iron availability is closely associated with bacterial virulence
  - Iron overload impairs immune function, thereby heightens susceptibility to and increases severity of infection

Vaziri et al, multiple publications
IRON & INFECTION in CKD
Iron overload impairs the Immune system

• ESRD $\rightarrow$ immune deficiency $\rightarrow$ increased risk of infection

• IV iron $\rightarrow$ compound uremia-induced immune deficiency
  - IV iron $\rightarrow$ intracellular ROS $\rightarrow$ shortens survival of CD4+ lymphocyte
  - IV iron $\rightarrow$ impair phagocytic activity and microbial killing capability of neutrophils

• lymphocytes are poorly equipped to sequester iron in ferritin $\rightarrow$ excess iron delivered by hydrophilic chelates can be toxic for lymphocytes

• iron overload $\rightarrow$
  - CD4+ T cell depletion
  - reduction of B cells, dendritic cells,
  - defective monocytes/neutrophils phagocytic capacity

  - Vaziri et al, multiple publications
Hospitalization Rates Due to Infection Have Increased in Hemodialysis Patients

USRDS analysis of period prevalent hemodialysis patients in 2011; rates adjusted for age, gender, race, & primary diagnosis; reference = ESRD patients in 2010

CV = cardiovascular.

Infection Is a Contributor to Mortality in the First Year of Dialysis

Adjusted cause-specific mortality in the first months of therapy:

Deaths per 1,000 Patient Years at Risk

Month Following the Initiation of Dialysis

Month 1: 21.8
Month 3: 47.1
Month 6: 30.6
Month 9: 25.3
Month 12: 24.1

Incident hemodialysis patients; adjusted for age, gender, race, & primary diagnosis.
Incident hemodialysis patients, 2005, used as reference cohort.

Iron & carotid artery lesions

- Carotid artery lesions in humans contain large amounts of iron, which strongly correlates with the plaque’s cholesterol and oxidized protein contents.

- In patients with carotid atherosclerosis serum ferritin level correlates with the level of low molecular weight iron compounds and lipid peroxidation products in the carotid endarterectomy specimens. (Vaziri et al, multiple publications)

- Interaction of iron and lipoproteins in the plaque promotes plaque instability by inducing foam cell apoptosis.

- RCT of mild iron reduction therapy (phlebotomy Q 6 months) in elderly patients with peripheral vascular disease (the “FeAST” trial) showed that Fe reduction strategy is safe and that it can reduce CV and overall M&M if initiated early but not late in the course of the disease. (Reduction of Iron Stores and Cardiovascular Outcomes in Patients With Peripheral Arterial Disease, A Randomized Controlled Trial, JAMA. 2007)
Common Carotid Artery IMT & Iron in Dialysis Patients

Drueke Study 2002: Cohort of 79 HD patients:
Cumulative iron dose was positively related to CCA-IMT ($P=0.015$) in patients <60 years.

Drueke et al, *Circulation* 2002
Potential role of iron in progression of renal disease

- Catalytically active iron accumulates in the renal tissue in various models of AKI
- Iron chelation therapy attenuates renal injury and dysfunction in these models
- Proteinuria results in accumulation of iron in the proximal tubular epithelial cells (most likely through uptake of filtered iron-binding proteins) causing cell damage
- Iron chelation therapy or iron deficient diet ameliorate proteinuria and improve renal function and structure in animal models of anti-GBM glomerulonephritis, puromycin-induced minimal change disease, membranous nephropathy and immune complex glomerulonephritis induced

- the role of iron in AKI, progression of CKD and potential loss of residual renal function in CKD and ESRD patients treated with excessive amounts of IV iron.

Vaziri et al, multiple publications
Potential role of iron in progression of renal disease


N=453 veteran men with NDD-CKD
Diagnose of Iron Overload in CKD
Diagnosis of Iron Overload in CKD: How do we know if there’s too much iron?

- Transferrin Saturation
  - Used in clinical practice globally
- Serum ferritin concentration
- Liver biopsy
  - Reference methodology (‘gold standard’)
- Magnetic resonance imaging (MRI)
  - Investigational, potential for broad access
TSAT in Different Disease States

The transferrin saturation index is calculated according the equation:

\[
\text{Saturation (\%)} = \frac{\text{serum iron}}{\text{TIBC}}
\]
Malnutrition-inflammation, by lowering serum transferrin level, may interfere with the reliability of the transferrin saturation ratio as a diagnostic tool for iron deficiency in dialysis patients.
Low TSAT $\rightarrow$ High Platelet Counts
in 40,787 HD Patients

Streja et al. *AJKD* Oct 2008
Ferritin

Single ferritin subunit

Ferritin protein consisting of 24 subunits

Cross section

U.S. National Library of Medicine
Serum Ferritin Alterations in Inflammation and Liver Disease

Ferritin>500 ng/ml = IL6 + TSAT
National Hemochromatosis Screening

“Any Ferritin over 200-300 ng/ml is a suspected case of hemochromatosis!”


But CKD Patients Are Different!

“...we suggest that the hemochromatosis criteria be modified for patients with ESRD.”

Almost 50% of Patients In the United States Have Ferritin Levels > 800 ng/mL*

OutcomesPlus National Provider Database, January 2009 through August 2011

Data from “OutcomesPlus database (Amgen); August, 2011.
Gold Standards: Liver Biopsy and Bone Marrow biopsy to measure iron content

• The “Gold Standard”
• Invasive
• Potentially risky
• Not often used in hematology
Magnetic Resonance Imaging

Measuring Hepatic Iron Content


Bright = high iron concentration; dark areas = low iron concentration

percutaneous liver biopsy with biochemical assessment of hepatic iron concentration (B-HIC) and liver with various gradient-recalled-echo (GRE) sequence
Current Day Evidence of Iron Overload

Hemodialysis-associated hemosiderosis in ESA era: MRI study

- Cross Sectional Analysis of 119 Chronic HD Pts
- 36 (30%) had "severe" iron overload of the liver (MRI) > 200 µmol/g

<table>
<thead>
<tr>
<th></th>
<th>Positive Control</th>
<th>High Iron HD</th>
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</thead>
<tbody>
<tr>
<td>Ferritin (µg/L)</td>
<td>524 (335-828)</td>
<td>2688 (1220–6820)</td>
</tr>
<tr>
<td>Liver Iron (µmol/g)</td>
<td>210 (70-280)</td>
<td>250 (210-340)</td>
</tr>
<tr>
<td>Hepcidin* (ng/mL)</td>
<td>ND</td>
<td>162.70 (5.29-1036)</td>
</tr>
<tr>
<td>Cardiac iron</td>
<td>ND</td>
<td>ND</td>
</tr>
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* Enzyme immunoassay, Peninsula Laboratories, USA; normal range: (1.71-175.9 ng/mL)


(adapted from presentation by J. Zaritsky, ASN 2013)
Current Day Evidence of Iron Overload
Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron.

- Targeted 21 with a serum ferritin >1000 μg/L
  - Ferritin 2688 ± 1489 μg/L
  - Hepcidin 60.15 ± 29.54 nM*
- Liver iron (via MRI)
  - 10% (n=2) had normal values (70 μmol/g)
  - 40% (n=8) had mild (80–90 μmol/g)
  - 25% (n=5) had moderate (90–95 μmol/g)
  - 30% (n=6) had severe (>95 μmol/g)
- NONE had iron overload in the heart

* mass spectrometry-based method; normal range: (10.61 ± 6.44 nM)

adapted from presentation by J. Zaritsky, ASN 2013)
Iron Overload and Survival in CKD
Is there an association between serum FERRITIN and DEATH in dialysis patients?
Risk of Death by Serum Ferritin Level
(time-dependent Cox model)

Risk of Death by Serum Ferritin Level (time-dependent Cox model)

N = 58,058 HD patients, 2001-2003

- Unadjusted Association due to STOP IV Iron at Ferr 800

K/DOQI zone: 100 - 800 ng/mL
Do-not-give-iron zone: >800 ng/mL

What about the association between serum FERRITIN and CARDIO-VASCULAR DEATH?
Risk of Death by Serum Ferritin Level
(*Cardiovascular Death*)

Risk of Death by Serum Ferritin Level (Cardiovascular Death)

N= 58,058 HD patients, 2001-2003

- Unadjusted
- Case mix
- Case mix and MICS

K/DOQI zone: 100 - 800 ng/mL
Do-not-give-iron zone: >800 ng/mL

What about the association between serum TSAT and DEATH?
Risk of Death by Transferrin Saturation Ratio (time-dependent Cox model)

N = 58,058 HD patients, 2001-2003

Effect of iron overload on survival in β-thalassaemia

Iron overload impairs survival in MDS

Malcovati, Haematologica, 2006
Administered IV Iron and SURVIVAL in 58,058 HD Patients

- 3 different IV irons were administered 2001-2003:
  1. Iron gluconate
  2. Iron sucrose
  3. Iron dextran

- All 3 forms of IV iron were merged into one single variable and 4 groups of HD patients were created:
  1. Those who did **not** receive any IV iron during the entire 13 weeks of baseline calendar quarter
  2. IV iron 1 - <200 mg/month
  3. IV iron 200 - <400 mg/month
  4. IV iron 400 mg/month or greater

Risk of Death by IV Iron Dose
N=58,058 HD patients, 2001-2003

Risk of Death by IV Iron Dose
N=58,058 HD patients, 2001-2003

CV Mortality Hazard Ratio

IV Iron Dose, mg/mo

Unadjusted
Case mix
Case mix and MICS

Did NOT receive IV iron (35% of patients)
Received IV iron: 65% of patients

Iron chelation
What is Chelation Therapy?

- Chelator
- Metal
- Toxic
- Non-Toxic
- "Chelate"

Outside the Body
Deferoxamine: Mode of Action

1. Dying RBCs
2. Reticuloendothelial cells
3. Free Iron
4. Heart
5. Liver
6. Endocrine Organs
7. Bile
8. Urine

Deferoxamine
- Unbound
- Bound

Excretion
Iron chelation and deferoxamine

• Chelation works by attaching a drug to iron, which allows the body to excrete it.
• Deferoxamine Rx is challenging…
  – Inconvenient and uncomfortable to take
  – Many unfavorable side effects
• …but it is effective
  – Enormous extension of lifespan in thalassaemia.
Deferoxamine works!

Survival of patients with thalassaemia

No similar data are available for iron chelation in CKD
Challenges of Deferoxamine

- Subcutaneous/Intravenous route of administration
  - Expensive
  - Cumbersome
  - Uncomfortable

- Rapid metabolism (30 minute half-life) necessitates prolonged infusion (12-15 hours)

- Complications due to iron overload still occur due to poor compliance with therapy
Common Side Effects of Deferoxamine

- **Local reactions**
  - Erythema (localized redness)
  - Induration (localized swelling)
  - Pruritus (itchiness)

- **Ophthalmologic**
  - Reduced visual acuity
  - Impaired color vision
  - Night blindness
  - Increased by presence of diabetes

- **Hearing loss**

- **Zinc deficiency**
Summary: Iron Overload in CKD

- Iron overload caused by transfusions or IV iron may lead to damage to the liver, heart, endocrine organs, bones, etc. CKD confounding effect is not clear?
- In the non-CKD population, the problems may begin after 30 units of PRBC (or even earlier). No contemporary data available in post-ESA era?
- In CKD, the use of ESA may have mitigated or even cured hemochromatosis?
- Higher TSAT associated with faster CKD progression?
- Serum ferritin level (>1200 ng/ml) and liver MRI may be used to estimate iron overload in CKD pts including HD pts?
- Therapy (chelation therapy) including IV iron withdrawal (while ESA RX is maintained) should be offered to iron overloaded CKD patients e.g. ferritin above 2,000 ng/ml range?
Why too much iron is a bad thing