Iron therapy in CKD—certainties and controversies

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Iron facts

• All body cells need iron.
• It is crucial for oxygen transport, energy production, and cellular growth and proliferation.
• The human body contains an average of 3.5 g of iron (males 4 g, females 3 g).
• The typical daily American or European diet contains 10–20 mg of iron.
• Only about 10% of dietary iron is absorbed (1–2 mg/day).

Daily iron loss is 1-2mg/day

Dietary iron

Utilisation

Muscle (myoglobin) (300mg)

Liver parenchyma (1000mg)

Duodenum (average, 1-2mg per day)

Plasma transferrin (3mg)

Storage iron

Utilisation

Other iron-containing enzymes (100mg)

Bone marrow (300mg)

Sloughed mucosal cells, desquamation, menstruation, other blood loss

Circulating erythrocytes (Hb) (1800mg)

Reticuloendothelial macrophages (600mg)

Iron loss 1-2mg/day

Anemia is frequent in patients with CKD

Cross-sectional, US multicenter survey of 5,222 adult patients at 237 physician practices

~60% of ND-CKD patients starting dialysis are iron deficient

Retrospective data from 1,997 patients starting dialysis 1999-2000 at 779 centers

Valderrábano F et al.  
Nephrol Dial Transplant 2003; 18: 89-100
“I can’t believe this! You’re low in iron.”
Stages of iron deficiency

- Depleted Iron Stores
  - Serrum ferritin
  - Transferin sat.
  - Erythrocyte ZPP
  - Hb
  - MCV
  - % HYPO
  - TfR
  - CHr or ret-HE

- Iron deficiency Normal Hb

- Iron deficiency Anemia

ZPP - zinc protophorphyrin
CHr or ret-HE – retikulocyte haemoglobin content
Iron Deficiency—Aetiology

- Increased demand for iron and/or haematopoiesis
- Iron loss
- Decreased iron intake or absorption
Causes of iron deficiency in ND-CKD patients

- Increased iron utilisation
  - ESA therapy
- Chronic inflammation
  - Inhibition of release of storage iron
- Blood loss
  - Gastrointestinal tract
  - Menstrual blood loss
  - Repeated venepuncture
  - Urinary blood loss (rare)
  - Surgical blood loss
- Malabsorption
  - Functional achlorhydria
  - Interfering medications e.g. phosphate binders
  - Chronic atrophic gastritis
- Dietary inadequacy

ND-CKD, non-dialysis chronic kidney disease; ESA, erythropoiesis stimulating agent
Iron Deficiency in Dialysis Patients

• Dialysis patients commonly suffer iron loss from:
  – gastrointestinal bleeding,
  – blood drawing,
  – and/or, most important with hemodialysis, the dialysis treatment itself.

• Hemodialysis patients lose an average of 1 to 2 g of iron per year.

• Thus, iron deficiency will tend to develop in virtually all dialysis patients unless supplemental iron therapy is given.

Estimated Annual Iron Losses in HD Patients

- Repeated laboratory test ~ 0.3g
- Accidental losses during HD ~ 1.0 g
- Blood retention in dialyzer and tubing ~ 1.0
- Normal iron losses ~ 0.4g
- **Total annual iron loss** ~ 2.7g

Increased need for iron during ESA therapy

- ESA increases the need for iron for synthesis of new red blood cells
- In the first 3 months of ESA therapy, a haemodialysis patient needs up to 30mg supplemental iron/24h (about 1000mg per month)
- Adequate iron availability increases erythopoiesis and reduces ESA requirements

ESA, erythropoiesis stimulating agent
Absolute & functional iron deficiency

**Absolute iron Deficiency**

- Depleted body iron stores
  - Low serum ferritin (<100ng/ml) or
  - TSAT <20%

**Functional iron Deficiency**

- Inadequate iron supply to meet demand e.g. during ESA therapy despite normal or abundant iron stores
  - Normal or high ferritin levels
  - TSAT <20%

ESA, erythropoiesis stimulating agent; TSAT, transferrin saturation
Wish JB. Clin J Am Soc Nephrol 2006; 1: S4-8
Iron and CKD

• Iron deficiency is an important contributor to anaemia in CKD

• Frequent causes of iron deficiency in ND-CKD patients include use of ESA therapy, blood loss, malabsorption and dietary inadequacy

• Iron deficiency is the leading cause of an inadequate response to ESA therapy in CKD

Optimal Therapy

- Route of administration
- Products
- Dose
- Safety
Iron therapy

• Oral

• Intravenous (i.v.)
ORAL IRON THERAPY

• Oral iron usually provides a safe, cheap and effective means of restoring iron balance in a patient with iron deficiency.

• There are a few simple principles governing the use of oral iron

• Iron salts should not be given with food because phosphates, phytates, and tannates in food bind the iron and impair its absorption

• A number of factors can inhibit the absorption of iron salts, including the use of antacids, certain antibiotics (eg, quinolones, tetracycline), and the ingestion of iron along with cereals, dietary fiber, tea, coffee, eggs, or milk.

• Iron should be given two hours before, or four hours after, ingestion of antacids.
Oral Iron is absorbed best from:
Causes of treatment failure in oral iron therapy

• Lack of adherence to therapy or insufficient length of therapy for the degree of iron deficit
• Concomitant/causal underlying blood loss pathology not resolved
• Poor duodenal absorption
• Side effects
  – Nausea
  – Constipation
  – Upper GI irritation
  – Diarrhea
• Iron refractory iron deficiency anemias (IRIDA)
Iron in Dialysis Patients

• Parenteral iron is routinely employed in dialysis patients for multiple reasons, including:
  – ongoing blood loss associated with the procedure,
  – the need for adequate iron to respond to the administration of erythropoietin,
  – as well as the frequent inability of these patients to utilize iron administered orally.
Risk of IV iron therapy

• Acute
  – Mild
  – Intolerance
  – Severe
    • Life treating anaphylaxis

• Mechanism
  – Allergic
    • To carbohydrate shell
  – Free iron?
Long term risks of chronic IV iron therapy

• Tissue iron overload
  – Hemosiderosis or hemochromatosis

• Increased infectious complications
  – Facilitates bacterial growth
  – Inhibitory leukocyte antibactericidal activity

• Cardiovascular disease and mortality
  – Pro-inflammatory cytokines
  – Oxidative stress
  – Lipid peroxidation
Iron and oxidative stress

Iron supplements

Colonic mucosa

Fenton reaction

Gasche C et al. UNI-MED Verlag, 2008
Long term risks of chronic IV iron therapy

• No prospective, controlled clinical trials show that IV iron increases risk of:
  
  – Hemosiderosis and hemochromatosis
  
  – Infection
  
  – Cardiovascular disease
  
  – Mortality
Iron Deficiency & Overload

Issues examined:

• Review definition of iron deficiency and how best to diagnose it

• Address definition and assessment of iron overload

• Discuss potential clinical consequences and patient level outcomes from iron overload
Iron Deficiency & Overload

General conclusions:

• Iron deficiency, particularly in the presence of anaemia, conveys poor prognosis, lower QOL/exercise capacity -- in CHF patients (CRS patients; also CKD?)

• No effective tests to diagnose iron overload

• Iron overload and its effects on other organ systems (liver, heart, pancreas, kidney) are generally rare

-- very different from haemochromatosis
Inflammation & Oxidative stress

Issues examined:

• How to measure oxidative stress

• How IV iron leads to oxidative stress/inflammation -- do infusion rates, dosages, or routes of administration affect the risk for oxidative stress?

• Address whether IV iron compounds promote atherogenesis and cardiovascular disease
Inflammation & Oxidative stress

General conclusions:

• Experimental data support the theory that IV iron promotes oxidative stress, inflammation, and atherogenesis

• Most clinical studies reporting such associations are observational and only prospective studies can clarify if these relationships are causal

• Currently there is insufficient evidence to take a position in recommending one iron preparation over another with respect to their potential for inducing oxidative stress
Iron & Infections

Issues examined:

• Assess the impact of iron administration on host immune function

• Examine possible links between IV iron and infection risk in CKD patients
Iron & Infections

General conclusions:

• Experimental data to indicate that iron can modulate host immune function (e.g., monocytes, neutrophils) but studies are conflicting

• Most epidemiological studies are observational in nature and there are limited data available on the cumulative iron doses to establish the association between iron usage and risks of infections
Hypersensitivity reactions to IV iron

Issues examined:

• Outline various characteristics of reactions (anaphylactic, mild, flares) to IV iron administration

• Determine if person-specific risk factors (e.g., pre-existing drug allergies) predict those at risk for hypersensitivity reaction

• Provide strategy for managing anaphylactic and minor infusion reactions to iron preparations
Hypersensitivity reactions to IV iron

General conclusions:

• All IV iron preparations can cause hypersensitivity reactions though risk of life-threatening reports remains rare and current available data cannot detect different differences in safety profiles of different formulations

• First dose should be administered in a clinical facility where trained staff and resuscitative equipment are available, but there is no physiological basis for the 30-minute post-infusion observation window

(as IV iron delivery should not be associated with a severe delayed reaction as seen with subcutaneous antigen presentation or in vaccination or allergen immune therapy)
Overall Conclusions

- The benefit/risk ratio of IV iron remains the same

- Preliminary consensus from the controversies conference suggests there is not sufficient new information that requires updating the current *KDIGO Anemia management guideline*

- The conference reinforced the importance of clinicians using the guidelines in clinical practice
Is the philosophy of iron therapy in dialysis patients moving to more safety?
Recent publications highlighted the problematic of iron therapy safety (1)

Epidemic of Iron Overload in Dialysis Population Caused by Intravenous Iron Products: A Plea for Moderation

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Iron toxicity: relevance for dialysis patients

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Iron dosing in kidney disease: inconsistency of evidence and clinical practice

Adam E. Gaweda1†, Yelena Z. Ginzburg2†, Yossi Chait3, Michael J. Germain4, George R. Aronoff4 and Eliezer Rachmilewitz5
Four recent epidemiological studies have shown similar adverse effects of excess iron loading in HD patients

- Dopps study: Bailie and coworkers Kidney Int 2015
- Ko-Lin Kuo and coworkers: PLOS One 2012
- Takahiro Kuragano and coworkers: Kidney International 2014
- Agarwal et al. KI 2015
Iron therapy - certainties

• We do need iron supplementation due to absolute and functional iron deficiency

• To provide substrate for ESA

• Iv iron in HD unit- convenient, efficaceous, the best possible patients adherence, spare costs of ESA
Figure 1: Potential risks and benefits of intravenous iron administration as compared with oral iron administration.
Controversies- oral vs intravenous

• In CKD- there is no final consensus in regard the route of administration

• the recent trial by Agarwal et al. (KI 2015) showed similar effects of oral and intravenous iron on hemoglobin levels and kidney function decline but more serious cardiovascular events and infections with intravenous iron.

• in FINDCKD compared with oral iron, IV FCM targeting a ferritin of 400-600 μg/L quickly reached and maintained Hb level, and delayed and/or reduced the need for other anaemia management including ESAs.

• Within the limitations of this trial, no renal toxicity was observed, with no difference in cardiovascular or infectious events.
Controversies

*Doses of iron required to correct iron deficiency*

• Since the true amount of iron loss in individual patients and patient groups is uncertain, the precise doses required to compensate for this loss inevitably remain uncertain. Applying doses of IV iron in excess of ongoing losses will result in positive iron balance, the consequences of which are unknown.
Controversies- iron and infections

• the evidence base for iron administration and risk of infection derives mostly from observational studies conducted in HD patients which are prone to confounding.
Controversies? Uncertainties?- ISS issue

• Rottemburg et al. showed the lesser efficacy of ISS when compared with brand, more ESA used (NDT 2011)
Future

- RCTs are urgently required to address the shortfall in the evidence base.
- An ongoing trial, PIVOTAL is recruiting 2080 HD patients across over 50 sites in the UK who will be randomized to a high-dose vs. a low-dose IV iron regimen with a planned follow-up of between 2 and 4 years.
- Hard endpoints such as death, myocardial infarction, stroke, heart failure, and infections will be assessed. In the meantime, nephrologists would do well to recognize broadly the benefits and the limitations of IV iron therapy, pending further robust scientific data.