Hepcidin and Iron Metabolism in CKD: What the Clinical Pharmacist needs to know!

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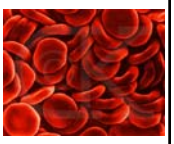
Case

- RW is a 68 yr old male (70 kg) on HD for the past 5 years secondary to DM.
- Access: fistula
- No significant complications
- Other comorbidities:
  - HTN
  - Dyslipidemia
  - CAD

Case

Labs:
- Hgb- 102g/L
- Tstat: 0.14; Ferritin: 542; Ret Count: 108 bil/L
- Vitamin B: 336 Red cell Folate: 1159
- Medications:
  - Darbepoietin 50mcg iv weekly
  - Iron Sucrose 100mg iv twice monthly
  - Amlodipine 10mg po daily
  - Ramipril 10mg daily
  - Atorvastatin 20mg po qhs
  - Replavite 1 tab po daily
  - $CaCO_3$ 1250mg-2 tabs tid with food.
  - Insulin: Humulin 30/70 12 u bid



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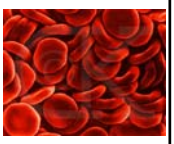


Case

- How do we treat his anemia?
  - Increase darbepoeitin?
  - Iron Load?
  - Both?
  - Do nothing?

Objectives

- Review Anemia Targets (Hgb and Iron indices)
- Review limitations of Iron Indices
- Understand molecular mechanisms of iron metabolism and RBC production
- Describe the role of hepcidin in iron metabolism and RBC production.

The Pathophysiologic Consequences of Untreated Anemia

Cardiac function[1]
Cognitive function[2]
Exercise and physical performance[3]
Health-related quality of life[4]

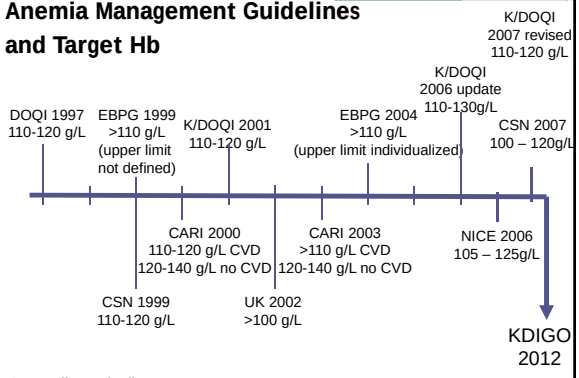
Increased cardiac output requirement[1,5]
LVMI[1,5]
Transfusion requirements[6]
Hospitalization[7,8]
Mortality[9,10]
Expenditures[8]

1. Levin et al. *Am J Kidney Dis.* 1999;34:125-134.
2. Nissenson. *Am J Kidney Dis.* 1992;20(1suppl1):S21-S24.
3. Mancini et al. *Circulation.* 2003;107:294-299.
4. Thadhani et al. ASN; November 1-4, 2002. Abstract and poster SU-P0820.
5. Foley et al. *Kidney Int.* 2000;58:1325-1335.
6. EPOGEN® (Epoetin alfa) [prescribing information]. Amgen, Inc; 2003.
7. Zawadzki et al. *Dis Manage Health Outcomes.* 2003;11:249-258.
8. London et al. *Am J Kidney Dis.* 2002;40:539-548.
9. Collins. *Adv Stud Med.* 2003;3(3C):S14-S17.
10. Al-Ahmad et al. *J Am Coll Cardiol.* 2001;38:955-962.

Chronic Kidney Disease and Anemia: Cardiovascular Double Jeopardy

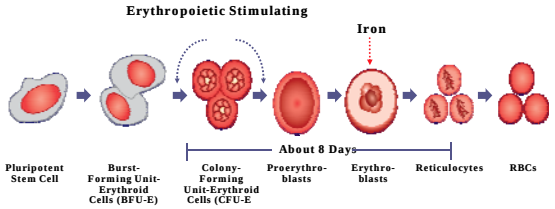
Study	Study Population	HCT/ Hb Target	CV Outcome	Quality of Life
Besarab *NEJM* 339:1998	HD + CHF/CAD	30 42	No difference	Improved
Foley *KI* 58:2000	HD-CHF/CAD	9.5-10.5 13-14	No difference	Improved
Roger *JASN* 15:2004	Stage 3-5	9-10 12-13	No difference	Improved
Parfrey *JASN* 16:2005	HD-CHF/CAD	9.5-11.5 13.5 -14.5	No difference	Improved
Levin *AJKD* 46:2005	Stage 2-5	9-10.5 12-14	No difference	Improved
Singh *NEJM* 355: 2006	Stage 4-5	11-11.5 13-13.5	Worse in high Hb	No difference
Druecke *NEJM* 355: 2006	Stage 4-5	11-11.5 13-15	No difference	Improved
Pfeffer NEJM 2009	Stage 3-5	130 vs 90	No difference (Increased stroke)	No difference

Anemia Management Guidelines and Target Hb



CVD=cardiovascular disease

RBC Production



Papayannopoulou T, et al In: Hoffman R, et al. *Hematology: Basic Principles and Practice.* 2005;267-288.
Weiss G, et al. *N Engl J Med.* 2005;352:1011-1023.

Anemia of CKD

Hyporesponse to EPO

- Consider:
  - iron deficiency
  - GI blood loss
  - infection/inflammation
  - hyperparathyroidism
  - malignancy
  - other anemias

Anemia of CKD

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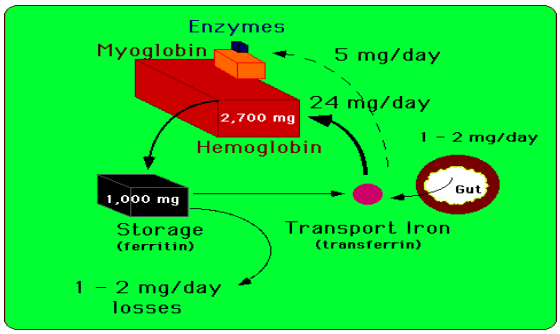
Anemia of CKD

- **When do we add iron?**
  - TSAT <20%
  - Ferritin < 200 (< 100 in CKD non dialysis)
- **How do we administer iron?**
  - Oral iron is tried first and usual practice for CKD 3-4
  - Iv iron preferred for HD pts

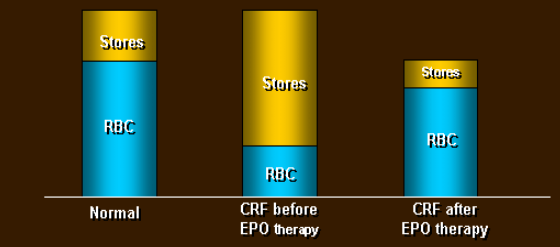
KDOQI 2007

Distribution of Body Iron



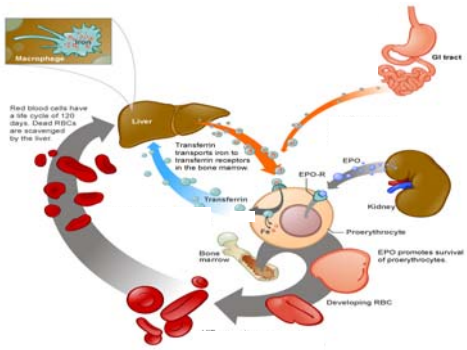
Andrews. NEJM 1999; 341: 1986-1995

Distribution of Body Iron (Before and After EPO Treatment)



Adapted from Cook and Eschbach. *Iron Metabolism and Its Disorders.* Excerpta Medica International Congress Series No. 366;1975;190.

Iron Traffic and Erythropoiesis



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KDOQI 2007

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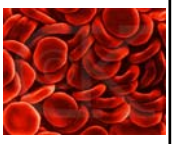


Issues with markers of iron deficiency anemia

"Functional" iron deficiency: ferritin is normal or high and Tsat is low

- Ferritin
  - acute phase reactant (increased in inflammation)
  - gender differences (lower in women)
- Tsat
  - decreased in inflammation (as transferin is elevated)
  - diurnal fluctuations

Kalantar-Zadeh. CJASN 2006; 1(suppl 1):S9:S-18

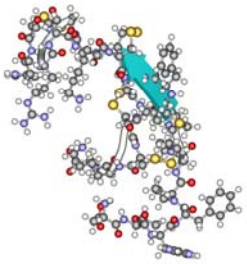
Anemia of CKD

Hyporesponse to EPO

- Consider:
  - iron deficiency
  - GI blood loss
  - infection/inflammation
  - hyperparathyroidism
  - malignancy
  - other anemias

Iron Balance, Inflammation and Erythropoiesis in CKD: HEPCIDIN

- **Hepcidin**
  - Hepatic bactericidal protein
  - Liver-expressed antimicrobial peptide (LEAP-1)
- **Hepcidin** small peptide hormone isolated from:
  - Human urine
  - Human blood
- **Hepcidin** exhibits antibacterial and antifungal activity



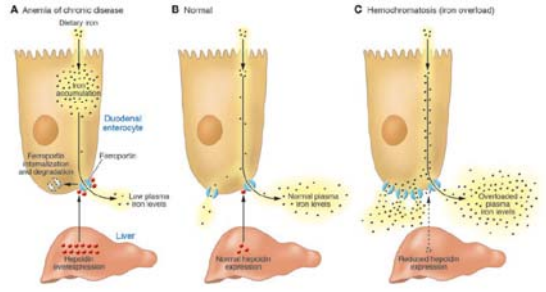
Park C, et al. J Biol Chem 2001; 276: 7806-7810; Krause A, et al. FEBS Lett 2000; 480: 147-150

Iron Balance, Inflammation and Erythropoiesis in CKD: HEPCIDIN

- Primarily produced and secreted by hepatocytes
- Key regulator of iron homestasis
- Hepcidin levels are regulated by different stimuli
  - Cytokines (inflammation)
  - Plasma iron
  - Anemia (iron deficiency)
  - Hypoxia
  - ESAs

De Domenico I. J of Clin Investigation 2007;117(7):1755-1758

Hepcidin-mediated regulation of iron homestasis



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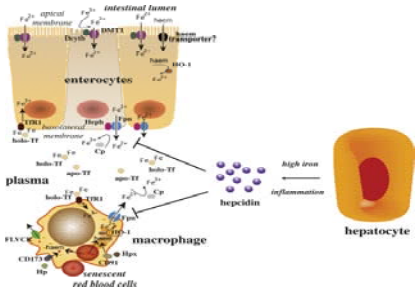

Pantopoulos, Wang. Biochem J 2011;434:365-381

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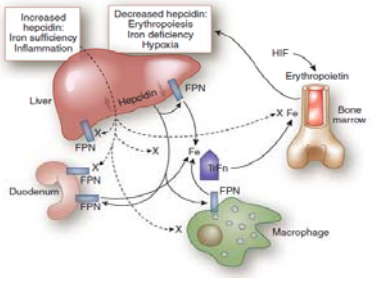
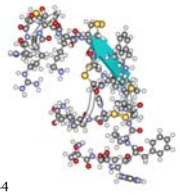


Coyne. KI 2011;80:240-244

Hepcidin-mediated regulation of iron homestasis

Increased Hepcidin	Decreased Hepcidin
• Iron sufficiency • Inflammation	• EPO (ie ESAs) • Iron Deficiency • Hypoxia



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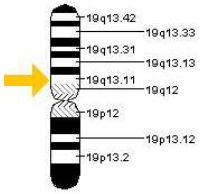
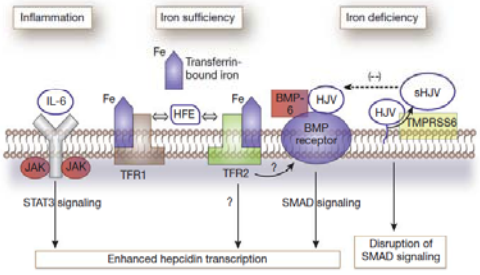
Hepcidin

- product of the *HAMP* gene
- The human *HAMP* gene is located on the long arm of chromosome 19

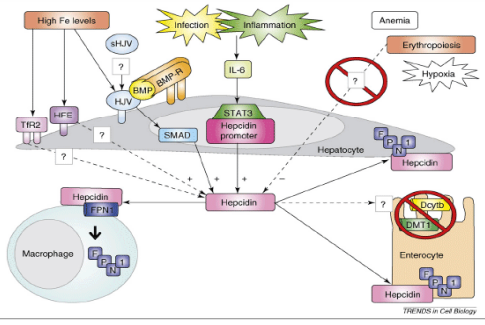


Signalling Pathways of Hepcidin



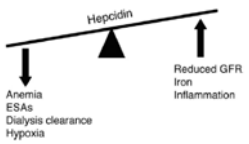
Babitt, Lin. AJKD 2010;55(4):726-741

Regulation of Hepcidin Synthesis



Hepcidin Levels in CKD

- Increased levels in pts with CKD by 2-4 fold and 6-9 fold in HD pts
- Studies have shown correlation with hepcidin levels and ferritin
- Issues with comparing assays and lack of standardization among methods.



Hepcidin as a Diagnostic Tool

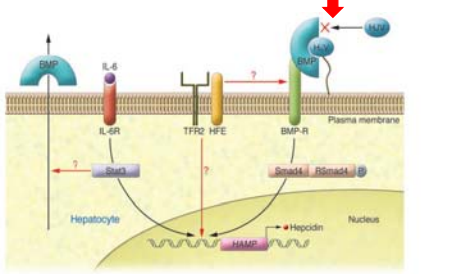
- Giving iron will increase hepcidin
  - Long-term effects??
    - Infections and oxidative damage?
    - Iron blockade?

Future of Hepcidin

- Administration of anti-hepcidin antibody
  - Mouse model but did not respond to iv iron
  - Inhibit transcription of hepcidin in preclinical studies
  - Human trials of this technology are expected

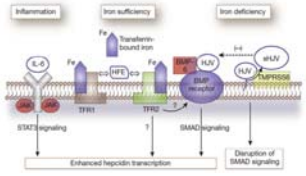
Future of Hepcidin

Dorsomorphin



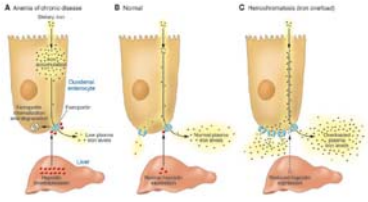
Future of Hepcidin

- Interruption of Il-6 activation of the hepcidin gene—toclilizumab lowers hepcidin levels but associated with increased infections
- Inhibition of Stat3- curcumin- decrease hepcidin production

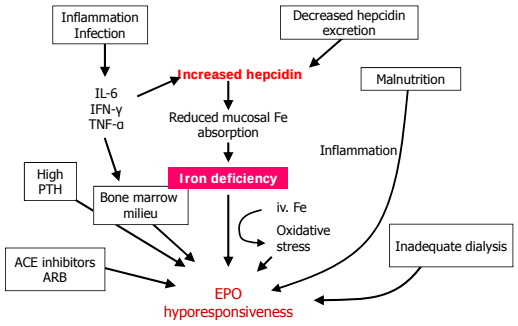


Future of Hepcidin

- Interruption of the binding of hepcidin to ferroportin



Summary: Anemia in CKD Patients



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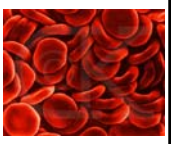

Conclusion

- Hepcidin is the key iron regulatory hormone
- Hepcidin is produced mainly in the liver
  - Its synthesis is stimulated by iron excess and inflammation
  - It is inhibited by anaemia, hypoxia and EPO
- Future Studies with Hepcidin
  - Used as a compliment to iron studies in renal anemia and anemia of chronic disease
  - Hepcidin antagonists to promote iron redistribution from macrophages to erythroblasts

Questions?