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MAGNET RECOGNITION

AMERICAN NURSES CREDENTIALING CENTER

Iron Overload in Sickle Cell Disease Review of Cause and Treatment

Susan M. Carson RN, MSN, CPNP
Nurse Practitioner III
Hematology Program
Children's Hospital Los Angeles

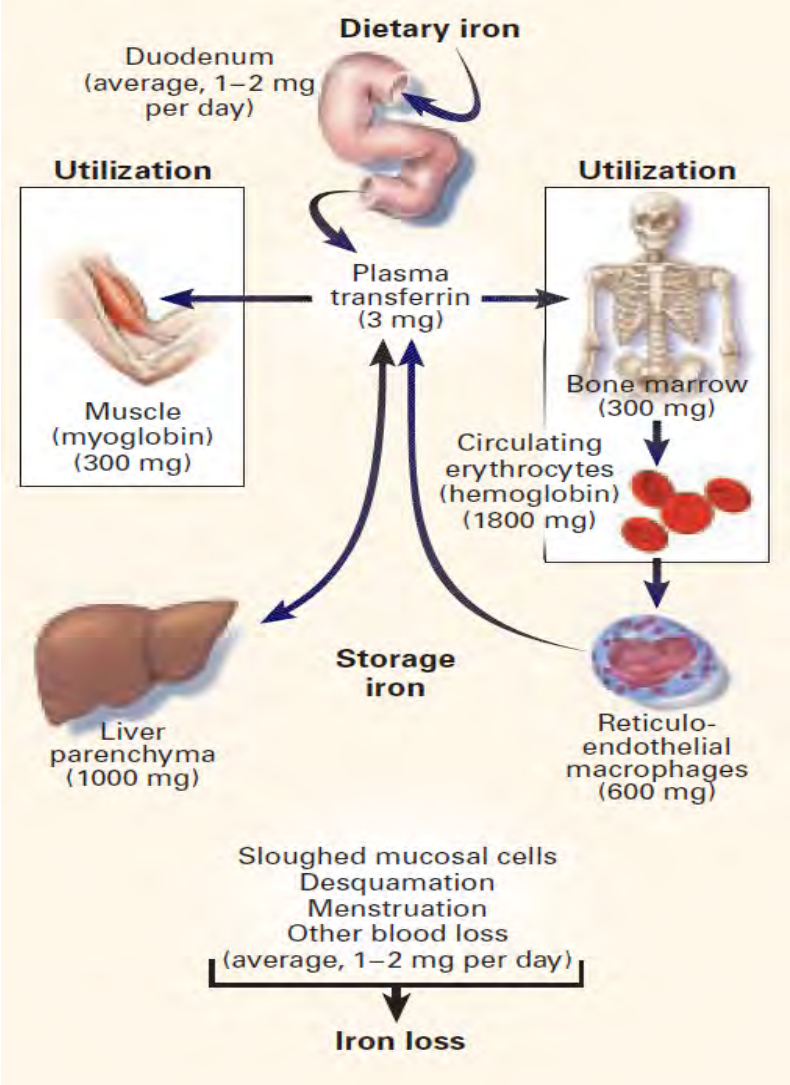
Objectives

- Describe the effect of iron overload on the various organs of the body in different disease states
- Understand the implications of iron overload facing sickle cell patients and their families
- Understand the medications used to treat iron overload- toxicities and side effects

Disclosures

- Member of the Novartis Speaker Panel for Exjade
- Advisory Board member and speaker for Apo-pharma
- Information will cover all current chelation therapies and will be fair and unbiased.
- Content will include off label use of pharmaceuticals

Normal Iron Metabolism



Why do we transfuse Sickle Cell patients?

- Primary and secondary stroke prevention
- ACS prevention
- Recurrent splenic sequestration
- Aplastic crisis
- Symptomatic anemia
- Preparation for surgery
- “bad disease”

Transfusions: the Benefit

- Safe
- Available
- Simple
- Improve the quality of life for the patient

Transfusions: The Cost

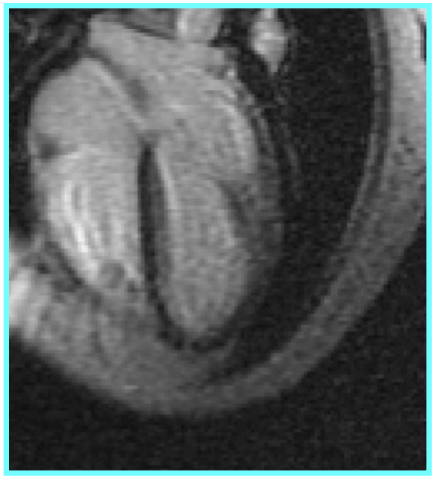
- Each unit of blood deposits 1 mg/ml (200-300 mg) of iron in the body
- Iron deposits in the liver, pancreas, thyroid, parathyroid, pituitary gland and heart
- Oxidative damage from iron causes tissue damage.
- **NO PHYSIOLOGICAL MECHANISM TO EXCRETE THE IRON!!**
- **Signs of iron overload after 10-20 transfusions**
- Multiple transfusions over time- chronic regimens or intermittent = iron overload

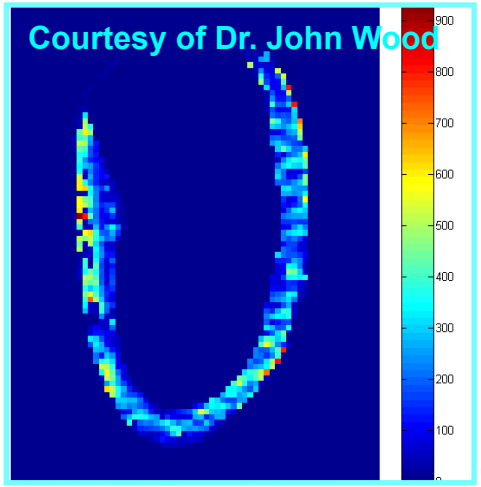
Measuring Iron

- **Direct measurements**
  - liver biopsy
  - MRI
- **Indirect measurements**
  - Serum ferritin
- **Invalid tools**
  - CT scan
  - Ultrasound.

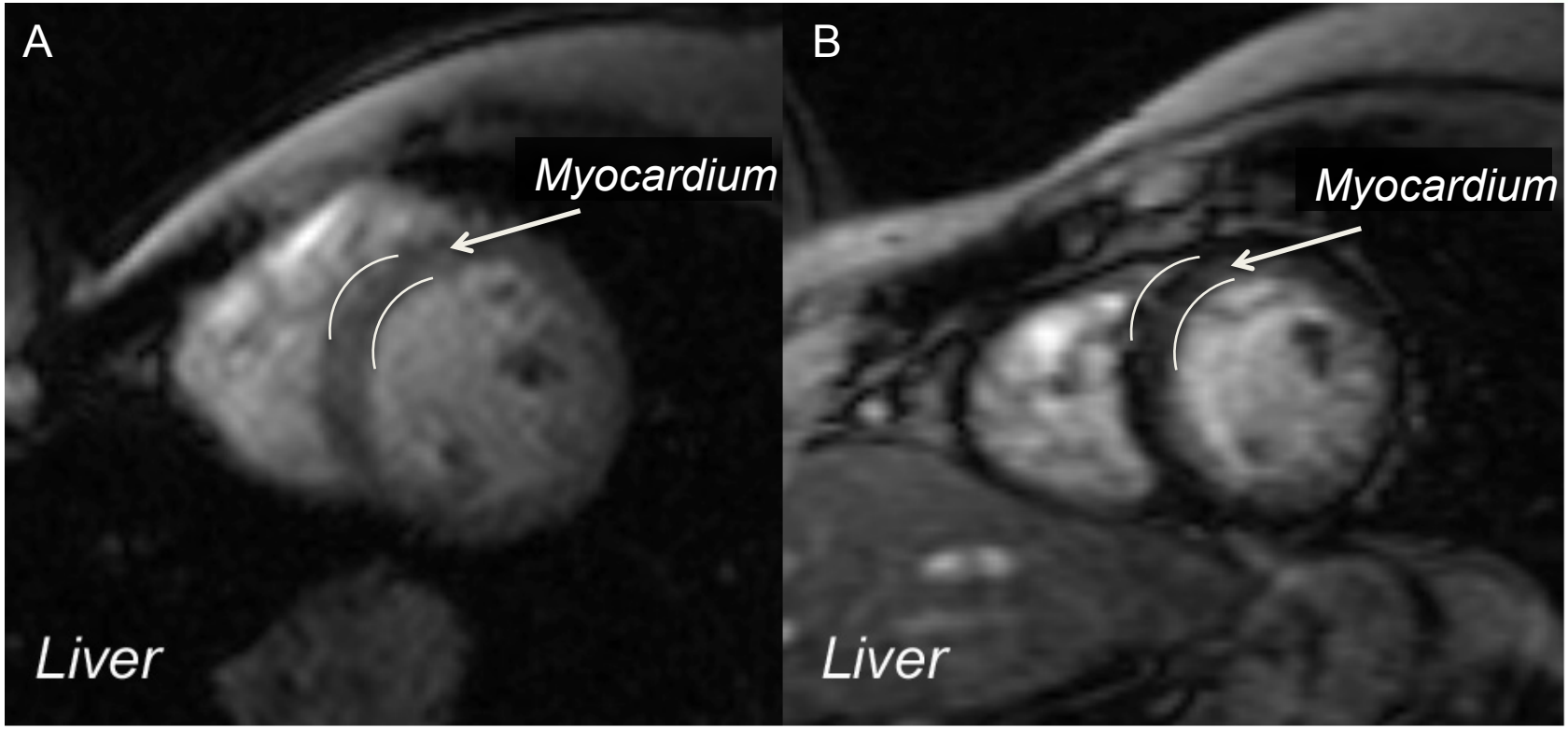
Measuring Iron: Cardiac / Liver iron by MRI (T2*)

- The Gold Standard
- Excellent correlation with liver and cardiac iron
- The only reasonable way currently to measure heart iron.
- Cardiac iron is not related to liver iron
- Requires special software





Liver iron does not directly correlate with cardiac iron



Black means high iron. In the MRI between A and B, the cardiac iron was high and the patient became adherent to chelation. Panel B shows the liver clears before the heart. (image courtesy of Dr J Wood)

Coates, TD, Free Radic Biol Med 2014 (in press)

Measuring iron: Ferritin as a Monitor of Chelation

- Advantages
  - Can be measured with every clinic visit
  - Widely available
  - Can examine trends over time
- Disadvantages
  - Loose correlation with liver (body) iron
  - Increased with inflammation
  - Decreased if scorbutic
  - Effect of chelation not linear
  - Different chelators may affect ferritin differently

DFO = deferoxamine.

Porter and Huehns. *Baillieres Clin Haematol*. 1989;2:459.

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Iron Toxicity ≈

Tissue iron X Environmental factors X Genetics X TIME

Iron: the Silent Killer

- Takes years for patients to have any symptoms
- The negative feedback comes when you are taking your chelator

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Goals of Chelation Therapy

- Protect cells from the damaging oxidant effects of Non Transferrin Bound Iron (NTBI)
- Prevent accumulation of NTBI and storage forms of iron
- Prevent or reverse iron induced organ damage
- Establish negative iron balance by removing iron from tissue and causing its excretion from the body.

NTBI- the culprit!

NTBI

is a shorter form of

Non-transferrin-bound iron

by allacronyms.com

Overview of iron chelators

Property	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox
Usual dose	25–60 mg/kg/day	75-100 mg/kg/day	20–40 mg/kg/day (Exjade) 14-28 mg/kg/day (Jadenu)
Route	s.c., i.v. 8–12 h, 5 days/week	p.o. 3 times daily	p.o. once daily
Half-life	20–30 min	3–4 h	8–16 h
Excretion	Urinary, fecal	Urinary	Fecal
Approved indications	Treatment of chronic iron overload due to transfusion-dependent anemias	Thalassemia major >18 years, second line therapy	Treatment of chronic iron overload due to frequent blood transfusions

s.c.= subcutaneous, i.v.= intravenous, p.o.= by mouth

Goals of treatment:

- Bind NTBI
- Normalize Total body Fe
- Clear abnormal tissue Fe
- Restore organ function

All have the same fatal defect:

None of these are effective if the patient does not take them

JADENU

- FDA approved 2015
- Film coated deferasirox tablets
- Same medication- same black box warnings and same monitoring
- Absorbed better- dosing is 30% less- 14 mg-28 mg/kg

  (vs 20-40 mg/kg for Exjade)
- 90 mg, 180 mg and 360 mg tablets.
- Taken once daily on an empty stomach or with a light meal
- Does not contain the sodium lauryl sulfate or lactose found in EXJADE (deferasirox) tablets for oral suspension – hope will be better tolerated with less GI side effects.
- Same price as Exjade
- Available at any specialty pharmacy- no EPASS system required

Chelation Side Effects - Management

- DFO- site reactions, allergy, rash, lesions
  - Site rotation, hydrocortisone, warm packs, increased dilution
- DFX- nausea, vomiting, diarrhea, rash, elevation in LFTs, renal toxicities
  - Start lower dose 20 mg/kg or 14 mg/kg (jadenu) and titrate up slowly
  - Dose reduction- or hold medication, take with food, mix with food, divide dose BID, take with lactaid
  - Less GI side effects with Jadenu formulation by clinical report
- DFP- nausea, vomiting, fatigue, arthralgia, neutropenia and agranulocytosis
  - Advise to start at 50% of dose and increase slowly over a few weeks
  - Hold if arthralgia, restart at lower dose and increase
  - Patients must have weekly CBCs to screen for neutropenia for 1st year at least
  - If patient has a fever- they MUST
    - Hold the drug
    - Go to the ED- tell them they are on a medication that can cause neutropenia

Treatment monitoring and dose modification

- Monitor total body iron (LIC)
  - LIC and cardiac T2* measurement approximately annually
  - Ferritin with each transfusion
  - Be very cautious making critical treatment decisions based on ferritin alone.
  - We use ferritin mainly to determine when we should get the next MRI
- Lower the LIC as fast as can be done safely.
  - In the absence of cardiac dysfunction, there is no dire emergency. Treatment response periods should be measured in 4 to 6 month periods.
  - However, be aggressive. You cannot predict when irreversible endocrine damage will occur.
  - Cardiac dysfunction due to iron overload is an emergency.
- Monitor organ function
  - Do not forget adrenal function. Patients can be severely adrenal insufficient. This diagnosis is easily missed and can be disastrously if not treated in the face of sepsis or cardiac dysfunction.
- Lack of response likely means they are likely not taking their medication
  - Otherwise, consider combination therapy

Combination Chelation

- Combination Chelation offers options for patients to:
  - Maximize 24/7 coverage
  - Intensify chelation for severely overloaded patients
  - Minimize side effects
  - Enhance compliance

- Sample “cocktails”
  - DFP/DFO- most studied
    - DFP daily, with DFO 3-7 nights/week
  - DFX/DFP- some studies
    - DFX- daily- even low dose, with DFO 3-7 nights/week
  - DFX/DFP- very little studies
    - DFP/DFX- both at full dose, or reduced depending on severity and tolerability

Chelation- overchelation

- DFO- truncal shortening, bone disease, auditory and ocular toxicities
- DFX: constipation, nausea, vomiting, renal tubular defects, alterations in electrolytes, increased LFTs, auditory and ocular toxcities
- DFP: increased LFTs
- Patients must be educated about what to look for and report
- Regular toxicity monitoring must be done as indicated for each drug.

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Final Thoughts

- Iron overload is an issue for many Sickle Cell patients
- Sickle Cell patients are not immune to the effects of iron overload
- Lifespans of iron overloaded patients have greatly improved thanks to MRI technology and increased chelation options.
- Never assume patients are compliant with their medical regimens- regardless of underlying disease
- Never ignore iron
- Each patient/family needs to be assessed and an individual plan tailored to that evaluation
- Having multiple chelators available allow for creative regimens that can maximize iron removal and compliance. Work with the patient to come up with something they can tolerate and maintain.

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Final, Final Thoughts

Contact Information.

Susan M. Carson

4650 Sunset Blvd

Los Angeles, CA

90027

323-361-4132

Scarson@chla.usc.edu