COULD/ SHOULD FERRITIN ALONE BE USED FOR MONITORING IRON OVERLOAD?

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September 2012
**ASSAYS OF SERUM FERRITIN (SF) FOR MONITORING IRON OVERLOAD (IO)**

- Cheap, noninvasive and widely available (*since 72*)
- Provides a measure of body iron stores.
- SF levels predict survival in thalassemia (*Oliveri et al, 1994; Borgna-Pignatti 2004*).
- **Trends in SF** levels track changes in total body iron in response to chelation (*Wood et al, 2011*)
  ...or phlebotomy (*Adams and Barton, 2011*)

..........but those are often deceiving (*Wood 2011*)
It ain't what you don't know that gets you into trouble.
It's what you know for sure that just ain't so
Mark Twain

Is what we know for sure that just ain't so?
what is: serum ferritin?

what is: iron overload?
CHEMICAL AND BIOLOGICAL PROPERTIES OF FERRITIN MOLECULES ARE KNOWN ONLY FOR CELL FORMS

Cytosolic: are hybrid molecules composed of variable proportion of H (with ferroxidase activity) and L chains (no ferroxidase activity):

Liver, spleen muscle heart, RBC

Faster Fe oxidation

testis, brain
Mitochondrial: homopolymers

FTHL17: stem cells and mostly nuclear

modified from P. Arosio
LIMITED KNOWLEDGE ABOUT THE BASIC PROPERTIES OF SERUM FERRITIN

We know that:
• SF is generally composed of L subunits.
• The proportion of H increases in malignant states.
• SF iron content is very low in Fe (<100 less than F) but rises (commensurately ?) with LIC in systemic IO.

We know little about:
• The cellular origin of SF in health and disease states,
• The triggers and mechanisms of SF “secretion” into plasma
• The potential cellular and/or systemic functions of SF.


Serum Ferritin: Past, Present and Future

Wei Wang¹, Mary Ann Knovich², Lan G. Coffman³, Frank M. Torti¹,⁵, and Suzy V. Torti⁴,⁵
what is:

SF
serum ferritin?

IO
iron overload?

“excessive” accumulation of iron but only labile iron is toxic!
**Systemic**

- Fluid and multiple organ IO
- hyperferremia
- hyperferritinemia

**Regional**

- Maldistribution regional IO/syst ID
- normo/hypoferremia
- hyperferritinemia

**SF**

- liver “responds” to NTBI (LPI) loading by synthesizing and secreting “excess” SF

**IO**

- accumulation:
  - plasma

**SHOULD FERRITIN ALONE BE USED FOR MONITORING IRON OVERLOAD?** NO! NO!

**SF**

- liver/RES “respond” to inflammatory and other signals by secreting SF

**Maldistribution**

- regional IO/syst ID
- normo/hypoferremia
- hyperferritinemia

** Accumulation:**

- Fluid and multiple organ IO
- hyperferremia
- hyperferritinemia

**Should Ferritin Alone be Used for Monitoring Iron Overload?** NO! NO!
Systemic IO

- hyperferremia
- hyperferritinemia
- plasma

Liver responds to TBI and NTPI by synthesizing SF and secreting “excess” via classical and non-classical secretory pathways

SF

marker for
- DIAGNOSIS
- TREATMENT

hemochromatosis (primary and transfusional)

SF is a surrogate marker of liver IO but not of impending organ IO

NTBI (or its labile component LPI) is an indicator of impending organ IO

HISTORY

COULD/SHOULD FERRITIN ALONE BE USED FOR MONITORING SYSTEMIC IRON ACCUMULATION AND ITS REMOVAL?
Liver iron concentration predicts total body iron stores

Liver Iron loading evokes ferritin secretion

\[ \text{Body iron (mg/kg)} = 10.6 \times \text{LIC (mg Fe/g dry wt)} \]

Stores calculated by quantitative phlebotomy.
LIC measured from biopsies in 25 patients.

\[ \text{Serum ferritin (µg/L)} \]

Wide response range.

\[ \text{Liver iron (µg Fe/g dry wt)} \]


Trends!
Different responses in rates of SF secretion vs LIC loading in various IODs

Trends show higher variance in SF-LIC relationship during chelation

Deferasirox, mg/kg/day

Change in LIC (mg Fe/g dw)

Change in ferritin (µg/mL)

n=325; R=0.63

wide response range

Studies 107 and 108
Mean SF, RBCm and NTBI (LPI) show similar but not parallel trends in beta-thal/HbE patients (N=40) under DFP chelation modified from Pootrakul P. et al. 2004 Blood 104 p. 1504

Trends are clear in population studies but variation of variation in SF are enormous.
Mean SF and LPI (NTBI) show similar but not parallel trends in MDS Low-/Int-1-risk under DFR chelation.

• Serum ferritin levels vary with transfusional rates, inflammation, and ascorbate status.

• Confidence intervals between ferritin values and true iron load are enormous.

• Low ferritin values do not guarantee organ IO and/or safety from the presence of labile/toxic iron (e.g. endocrine or cardiac iron).

Thal E-β transfusion-dependent for 10 yrs, DFO treated

• Cardiac T2* 2 ms
• LVEF 48%
• HIC 18.8 mg/g
• SF 248 ng/ml

(Wood 2011)
Sequence of changes of iron status during loading and chelation

Iron unloading

- Organs
- NTBI (LPI)

Iron loading

- DFP
- DFO
- TBI
- LIC
- SF

No relationship between organs and liver (or SF)
Trends in IO can markedly differ between heart and liver

Noetzli et al, Blood, 2009
Trends in Ferritin Can Be Dramatically Different From Trends in Total Body Iron and Could Lead to Erroneous Decisions in Iron Chelation Management and Discourage Adherence in Chronically Transfused Patients


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2011- ASH Annual Meeting and Exposition (San Diego)
SF and LIC trends in individual patients

Single patient example showing similar trends of ferritin and LIC between 2003 and 2007 (A) and divergent trends thereafter (B).

From: M. Puliyel et al ASH Ann Meeting 2011
Evolution of acceptance of serum ferritin as **sole** reliable marker of iron overload in hh and th?

GOOD

NOT BAD

NOT SO BAD

NOTHING BETTER

the 1\textsuperscript{st} 20 years

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the 2\textsuperscript{nd} 20 years?

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GOOD BUT NOT ALONE
2006
The Fascinating but Deceptive Ferritin: To Measure It or Not to Measure It in Chronic Kidney Disease?

2008
Serum Ferritin: Deceptively Simple or Simply Deceptive? Lessons Learned From Iron Therapy in Patients With CKD

2010

2012

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