Blood Donation and Iron Reserves: Current Issues and Advances

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SANBTC, Sun City, S.A.
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Committee members agreed that iron depletion in blood donors is a concern.

Discussed testing for iron status in the donor setting.

Discussed alternative strategies to mitigate iron depletion:
- Iron supplementation, dietary recommendations
- Changing Hb/hct acceptance standards
- Modification of interdonation interval
Underlying issues

- Donation (including apheresis) removes iron
- Iron is not readily replaced
- Low hemoglobin (Hb) is a late effect of iron depletion
- Hb cutoffs and interdonation intervals are somewhat arbitrary
- Impacts of iron deficiency are not well-documented
- Sex, age, and BMI all impact the effects of donation
Iron loss following blood donation

- Iron loss following blood donation ~ 200-250mg
- Premenopausal women have lower iron stores than men
- Frequent blood donations deplete iron stores
- Replacement of lost iron is dependent on exogenous sources
## Definitions of anemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Hemoglobin levels below which 5% of the normal subjects in the population will be found (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White men 20 -59</td>
<td>13.7</td>
</tr>
<tr>
<td>Black men 20-59</td>
<td>12.9</td>
</tr>
<tr>
<td>White women 20-49</td>
<td>12.2</td>
</tr>
<tr>
<td>Black women 20-49</td>
<td>11.5</td>
</tr>
</tbody>
</table>

NHANES III and Scripts –Kaiser databases

Blood. 2006 Mar 1;107(5):1747-50
NHANES II data: Hb concentrations in men 18 to 44 years of age. (◆) Caucasian men; ( ░ ) African American men.

Hemoglobin distribution in women

NHANES II data: Hb concentrations in women 18 to 44 years of age. (◆) Caucasian women; (■) African American women.

### International donor Hb levels (g/dL)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Hb-male</th>
<th>Hb-female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Council of Europe</td>
<td>13.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Australia</td>
<td>13.0</td>
<td>12.0</td>
</tr>
<tr>
<td>UK</td>
<td>13.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Health Canada</td>
<td>12.5</td>
<td>Both Sexes</td>
</tr>
<tr>
<td>FDA Current</td>
<td>13.0</td>
<td>12.5*</td>
</tr>
</tbody>
</table>

* Female Hb may be changed to 12.0 with FDA-approved procedures
## International standards

<table>
<thead>
<tr>
<th>Country</th>
<th>Minimum hemoglobin</th>
<th>Interdonation interval or frequency per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>12.5 for women</td>
<td>56 days</td>
</tr>
<tr>
<td></td>
<td>13.0 for men</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>12.5</td>
<td>56 days</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>12.5 for women</td>
<td>112 days</td>
</tr>
<tr>
<td></td>
<td>13.5 for men</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>12.0 for women</td>
<td>84 days</td>
</tr>
<tr>
<td></td>
<td>13.0 for men</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>12.5 for women</td>
<td>Women: 18 weeks, 3x/year</td>
</tr>
<tr>
<td></td>
<td>13.5 for men</td>
<td>Men: 10 – 11 weeks, 5x/year</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>11.5 for women</td>
<td>Women: 3x/year</td>
</tr>
<tr>
<td></td>
<td>13.0 for men</td>
<td>Men: 4x/year</td>
</tr>
</tbody>
</table>
Studies of iron stores and donation frequency

- High prevalence of iron deficiency in frequent blood donors
  - REDS II donor iron study
- Repeat donations lead to decreased serum ferritin in male and female donors
- Clear correlation of iron deficiency with frequency of donation
- Depletion of iron stores occurs gradually with increased frequency of blood donation
Effect of donation frequency on hemoglobin and iron status

Hb (g/dL) for both genders at four donations without iron supplement (red = women, blue = men).

Serum ferritin (μg/L) for both genders at four donations without iron supplement (red = women, blue = men).
**REDS-II Donor Iron Status Evaluation - RISE**

- 4 cohorts of donors – First-time/reactivated and frequent donors (males and females)
- 2425 donors total – characterized and followed for up to 2 years
- At enrollment their ferritin, soluble transferrin receptor (sTfR) and hemoglobin were measured
- Two measures of iron deficiency: **AIS** / Absent iron stores [ ferritin<12 ng/mL ] and **IDE** / iron-deficient erythropoiesis [ log(sTfR/ferritin)≥ 2.07 ]

Fig. 1. Effect of 12-month whole blood or RBC donation frequency on venous Hb by males (▲) and pre- (◆, age < 50 years) or postmenopausal (■, age ≥ 50 years) females.

Cable et al, Transfusion 2011;52: 511-522
Fig. 2. Effect of 12-month whole blood or RBC donation frequency on the geometric mean of plasma ferritin by males (▲) and pre- (◆, age < 50 years) or (■, age ≥ 50 years) postmenopausal females.

Cable et al, Transfusion 2011;52: 511-522
TABLE 1. Medians (2.5%-97.5% range) for venous Hb, ferritin, sTfR, and log(sTfR/ferritin) and proportion with AIS and IDE by enrollment cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Hb (g/dL)*</th>
<th>Ferritin (ng/mL)</th>
<th>sTfR (mg/L)</th>
<th>Log(sTfR/ferritin)</th>
<th>AIS (%)</th>
<th>IDE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT or RA</td>
<td>13.3 (11.5-15.2)</td>
<td>37 (9-175)</td>
<td>2.7 (1.7-4.8)</td>
<td>1.8 (1.1-2.6)</td>
<td>6.4</td>
<td>24.7</td>
</tr>
<tr>
<td>Frequent</td>
<td>13.2 (11.4-15.2)</td>
<td>19 (5-68)</td>
<td>3.1 (1.8-6.6)</td>
<td>2.2 (1.5-3.0)</td>
<td>27.1</td>
<td>66.1</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT or RA</td>
<td>15.1 (12.8-17.4)</td>
<td>108 (29-430)</td>
<td>2.7 (1.6-4.4)</td>
<td>1.4 (0.8-2.1)</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>Frequent</td>
<td>14.5 (12.0-16.6)</td>
<td>25 (6-117)</td>
<td>3.1 (1.8-8.0)</td>
<td>2.1 (1.3-3.1)</td>
<td>16.4</td>
<td>48.7</td>
</tr>
</tbody>
</table>

* Post vHb samples were converted to predonation values using the formula Pre vHb(g/dL) = Post vHb + 0.8423 – (0.002035 × weight [lb]).
### Proportion with AIS and IDE at Enrollment

<table>
<thead>
<tr>
<th></th>
<th>AIS (%)</th>
<th>IDE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
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<td>FT or RA</td>
<td>6.4</td>
<td>24.7</td>
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<td>27.1</td>
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<td><strong>Males</strong></td>
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<td>48.7</td>
</tr>
</tbody>
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- Donation intensity in the past two years had the biggest association with AIS and IDE.
- Females, younger and/or menstruating donors and those with lower weight were also more likely to have either AIS and/or IDE.
- Marginally significant variables included being a non-smoker, previous pregnancy and not taking iron.

Iron Replacement Study at the NIH Clinical Center

- Hgb deferred donors and iron deficient control donors offered iron replacement
- Donors given iron had “steady and consistent improvement and normalization of iron-related laboratory parameters” even when they continued to donate
- Iron was well tolerated with 68% compliance and 21% adverse GI effects

- Bryant et al. (2012) Transfusion, vol. 52; 1566-75.
Australian Red Cross Study

- Female returning whole blood donors aged 18-45 were randomized to receive an 8 week post-donation course of carbonyl iron (45 mg)
- At week 12, the proportion of iron deficient donors was 51.9% in the iron group and 80.5% in the placebo group, and mean Hgb was significantly higher in the iron group

HEIRS Study

Study population: 215 eligible donors, 18-79yo, no donation for ≥ 4 months

| Table 1. Baseline Characteristics of Study Participants by Ferritin Level |
|--------------------------------------------------|------------------|------------------|------------------|------------------|
|                                           | Low Ferritin (≤26 ng/mL) | Higher Ferritin (>26 ng/mL) |
|                                           | Iron (n = 51) | No Iron (n = 50) | Iron (n = 60) | No Iron (n = 54) |
| Women, No. (%)                               | 33 (64.7) | 31 (62.0) | 38 (63.3) | 34 (63.0) |
| Age ≥60 y, No. (%)                           | 12 (23.5) | 11 (22.0) | 17 (28.3) | 12 (22.2) |
| Age, mean (SD), y                            | 47.5 (15.5) | 45.9 (15.7) | 49.3 (14.6) | 48.1 (14.6) |
| Weight, mean (SD), kg                        | 75.9 (16.4) | 76.8 (15.8) | 81.5 (16.4) | 77.9 (16.2) |
| Hemoglobin, mean (SD), g/dL                 | 13.2 (1.0) | 13.7 (1.3) | 14.1 (1.0) | 14.3 (1.2) |
| Ferritin, mean (SD), ng/mL                  | 14.9 (5.8) | 15.2 (6.0) | 54.0 (24.3) | 58.9 (32.9) |
| sTfR, mean (SD), mg/L                       | 4.0 (1.33) | 3.9 (1.19) | 3.1 (0.65) | 3.1 (0.62) |
| Estimated blood volume, mean (SD), L        | 4.59 (0.8) | 4.66 (0.91) | 4.79 (0.84) | 4.64 (0.84) |

Kiss et al, JAMA 2015;313:575-583
A Hemoglobin level over time since blood donation

Kiss et al, JAMA 2015;313:575-583
**B** Hemoglobin level as percentage of baseline

![Graph showing hemoglobin level over time for different conditions]

- **Higher ferritin (>26 ng/mL)**: Received Iron supplements, No Iron (indicated by different symbols
- **Low ferritin (≤26 ng/mL)**: Received Iron supplements, No Iron

*Time since donation, d*

Kiss et al, JAMA 2015;313:575-583
<table>
<thead>
<tr>
<th>Ferritin Group (ng/mL)</th>
<th>No. of Participants</th>
<th>Time to 80% Hemoglobin Recovery, Mean (IQR), d\textsuperscript{a}</th>
<th>(95% CI)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Low (≤26)</td>
<td>30</td>
<td>36 (33-39)</td>
</tr>
<tr>
<td>Iron</td>
<td>Higher (&gt;26)</td>
<td>29</td>
<td>32 (29-34)</td>
</tr>
<tr>
<td>No iron</td>
<td>Low (≤26)</td>
<td>30</td>
<td>153 (126-&gt;168)</td>
</tr>
<tr>
<td>No iron</td>
<td>Higher (&gt;26)</td>
<td>29</td>
<td>92 (76-130)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Low (≤26)</td>
<td>17</td>
<td>25 (23-28)</td>
</tr>
<tr>
<td>Iron</td>
<td>Higher (&gt;26)</td>
<td>20</td>
<td>30 (27-35)</td>
</tr>
<tr>
<td>No iron</td>
<td>Low (≤26)</td>
<td>18</td>
<td>&gt;168 (102-&gt;168)</td>
</tr>
<tr>
<td>No iron</td>
<td>Higher (&gt;26)</td>
<td>20</td>
<td>68 (50-95)</td>
</tr>
</tbody>
</table>
Study procedures; Male apheresis donors

• 3/01/2016 start in 3 regions, rolling start across 5 additional regions over 2.5 months
Retention tube sent to Scientific Support Office (SSO) for ferritin testing for male plateletpheresis donors with Hb b/w 12.5 - 13.4 g/d


• Ferritin results and letter preparation managed by SSO staff

• Donor management:
  • donors with ferritin ≤ 26 ng/mL sent “low ferritin” letter and removed from TR list for 4 weeks
  • existing appointments not canceled
  • “low-ferritin” letter sent initially and at minimum of 90-day interval subsequently

(Courtesy Bryan Spencer)
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  - existing appointments not canceled
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(Courtesy Bryan Spencer)
## Correlates of low iron stores -- I

(Courtesy Bryan Spencer)

<table>
<thead>
<tr>
<th>SDP donation frequency at enrollment (prior year)</th>
<th>N</th>
<th>Ferritin % &lt; 12</th>
<th>Ferritin % ≤ 26</th>
<th>OR&lt;sub&gt;Ferr≤26&lt;/sub&gt;</th>
<th>Adjusted OR&lt;sub&gt;Ferr≤26&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 5</td>
<td>1379</td>
<td>19%</td>
<td>41%</td>
<td>0.68 (0.52, 0.89)</td>
<td>0.62 (0.52, 0.74)</td>
</tr>
<tr>
<td>6 to 10</td>
<td>909</td>
<td>18%</td>
<td>50%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>11 to 15</td>
<td>790</td>
<td>25%</td>
<td>63%</td>
<td>1.71 (1.25, 2.35)</td>
<td>1.76 (1.44, 2.15)</td>
</tr>
<tr>
<td>16 to 24</td>
<td>976</td>
<td>28%</td>
<td>70%</td>
<td>2.31 (1.70, 3.15)</td>
<td>2.63 (2.17, 3.20)</td>
</tr>
</tbody>
</table>

### Ferritin %

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>N</th>
<th>Ferritin % &lt; 12</th>
<th>Ferritin % ≤ 26</th>
<th>OR&lt;sub&gt;Ferr≤26&lt;/sub&gt;</th>
<th>Adjusted OR&lt;sub&gt;Ferr≤26&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5-12.9</td>
<td>538</td>
<td>29%</td>
<td>62%</td>
<td>1.38 (1.06, 1.80)</td>
<td>1.35 (1.10-1.65)</td>
</tr>
<tr>
<td>13.0-13.4</td>
<td>3516</td>
<td>21%</td>
<td>53%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Summary observations

- Blood donation impacts iron stores
- Frequent donation leads to IDE or AIS
- Recovery time from a single donation is greater than allowable IDIs
- Modest iron replacement will accelerate recovery
- Specific groups are at greater risk
  - Frequent donation (WB and pheresis)
  - Young (school-age) donors
  - Female donors of child-bearing age
  - Donors with low but acceptable Hb levels
  - Male donors may have prolonged recovery of iron levels
Effects associated with iron deficiency

- Cognitive dysfunction
- Fatigue
- Pregnancy-related complications
- Decreased exercise endurance
- Pica
- Restless-leg syndrome
- Anemia

(Note: Some blood-bankers point out that these outcomes are not routinely observed among donors)
AABB Association Bulletin 17-02

- Blood establishments should develop policies to limit or help prevent iron deficiency in their donors
- Educational materials
- Interventions for those at-risk
- Monitor impact of measures

Educational materials

- Alert donors to risk of iron deficiency
- Relevance to those at higher risk
- Benefits of iron replacement post-donation
  - Type of Fe, dosage, period of supplementation
- Note problems re GI blood loss, hemochromatosis etc.
- Consult health-care provider re Fe and other medications

- Even specifically directed educational material has had little impact, however
At-risk groups considered for interventions

- Young donors (*at minimum, 16-18*)
- Premenopausal females
- Frequent donors
  - Male: 3 or more donations in 12 months
  - Female: 2 or more donations in 12 months
- Donors with Hb near level for eligibility eg:
  - Males: 13.0-13.5 g/dL
  - Females: 12.5-13.0 g/dL
Recommended interventions

- Donor iron supplementation
  - At least 18mg elemental iron daily for 60 days
- Lengthening IDI and/or decreasing donations per year
  - 56-day interval leads to negative iron balance
  - If no other intervention, no more than 2 donations/year
  - (Young donors 1/year)
  - Will reduce blood availability, consider additional interventions
- Donor ferritin testing to support other actions
  - All donors or subgroups
  - Advise those with low values on Fe supplementation and/or donation frequency
  - Collect at time of donation: actions relate to future donation (effective POC tests not available)
Some Disadvantages of Giving Iron to Donors

• Cost of supplements
• Time to manage and monitor such a program
• Possible side effects of iron supplementation
• Donor willingness to take supplements
• Medical implications of masking conditions such as cancer or exacerbating hemochromatosis
What is happening?

• Limited actions implemented or under consideration
• More attention to Hb deferrals
  • Education
  • Extended deferral
  • Ferritin
• Management of at-risk groups
  • Young donors: ferritin, extended IDI (particularly for Hb deferral)
  • Frequent donors
  • High-frequency donors
Summary

• Recognition that iron deficiency is common among blood donors
• Hb deferral reflects a late response to iron deficiency
• Iron recovery takes more time than frequently-used interdonation intervals
• Iron replacement accelerates recovery
• New recommendations and regulatory requirements
• Ferritin testing may be best approach to management
• However, test results only obtained post-donation
• We are responsible for donor health and safety
Acknowledgements

• I am grateful to the following for assistance and for sharing slides
  • Susan Stramer
  • Bryan Spencer
  • Whitney Steele