Iron depletion in frequently donating whole blood donors

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Iron: relevance

• oxygen-transporting and storage proteins
  – hemoglobin and myoglobin
• iron-containing centers in many enzymes
  – mitochondrial respiratory chain
  – DNA-synthesis
• immune system: regulatory functions
  – immune cell proliferation
  – cytokine activities (e. g. IFN-γ effector pathway)
Depletion in storage iron

• Iron deficiency (ID)
  – Iron depletion phase (prelatent ID)
    ♦ reduced iron stores
  – Iron deficient erythropoiesis (latent ID)
    ♦ serum iron (functional department) decreased
    ♦ iron deficient erythropoiesis, no anemia
  – Iron deficiency anaemia
    ♦ Hb < 12 g/dL (♀), < 13 g/dL (♂) [WHO]
Iron deficiency: symptoms

• Iron deficiency anemia
  – Impaired physical capacity
    • reduced tissue oxygen

• Non anemia related symptoms
  – Impaired cognitive function
    • Impaired attention span
    • Decline of short term memory
    • Impaired learning ability
    • Impaired cognitive function
  – Impaired athletic performance
Iron loss from blood donation

• 1ml blood contains about 0.5 mg of iron
• Whole blood donation:
  – collection volume: 495 ml + 30 ml
  – loss of 220 - 290 mg iron, corresponding to about 6% (male) and 10% (females) of total body iron
• Plasmapheresis:
  – blood volume lost: 15 ml + 30 ml
  – loss of 20 - 25 mg iron
Iron balance

- dietary iron: 10 - 20 mg / day
  - only 20% of dietary iron is absorbed
  - maximum iron absorption: 3 – 4 mg/day
  - physiological iron loss:
    - 1 mg/day in men and postmenopausal women
    - additional 0.5 (- 1.2) mg/day in menstruating females
Compensating iron loss from blood donation

- iron compensation / donation interval:
  - 80 – 120 days (♂), 110 – 150 days (♀)
  - Minimum donation interval according to German guidelines: 2 months (♂) or 3 months (♀)
  - negative iron balance at more than 3 – 4 donations (♂) or 1 – 2 donations (♀) per year

- incidence of iron deficiency in regular blood donors:
  - up to 20% in male donors
  - up to 40% in female donors
Responsibilities of Transfusion Medicine

• sufficient blood supply
  – optimal „utilization“ of volunteers willing to give blood

• donor safety
  – determination of Hb prior to blood donation
  – deferral of donors with iron deficiency anemia
    • (permanent) loss of donors due to short term deferral
  – compensation of iron loss by supplementation
    • adverse effects of iron medication (GI-system 20%)
    • missing underlying disease (hemochromatosis, GI-bleeding)
    • change in blood center - donor relationship
Prevention of iron deficiency by iron supplementation

- studies on menstruating women:
  - administration of 39 mg of elemental iron daily allowed menstruating woman to donate every 8 weeks without significant iron depletion (Simon et al. 1984)

- iron compensation with a lower dose possible?

- can donation frequency or volume be increased?
Laboratory evaluation of body iron

• Serum Ferritin
  – intracellular iron storage protein
  – Serum ferritin level correlates with body iron stores
    ✷ 1 µg/l equivalent to 8 -10 mg of storage iron
    ✷ Ferritin < 12 µg/l: indicate complete depletion of iron stores
  – acute phase reactant: false high values in malignancies, infections, liver disease

• Serum Transferrin Receptor (TfR)
  – proportional to cellular expression of the transferrin receptor
  – reflects functional iron compartment / iron-deficient erythropoiesis
  – assay is not standardized!
$\log(\text{TfR/F})$

- quantitative phlebotomy
- inverse linear relationship between logarithm of the ratio of the soluble transferrin receptor to ferritin concentration (TfR/F) and body iron

Skikne et al. Blood. 1990;75:1870-1876
Iron supplementation in blood donors (1) study design

- placebo-controlled, double-blind study
- 526 regular blood donors (289 ♂, 237 ♀)
  - iron supplementation:
    - 40 mg, 20 mg or 0 mg per day of elemental iron (ferrous-gluconate)
    - ascorbic acid and other vitamins
  - whole blood donation:
    - 4 donations every 8 weeks (♂)
    - 3 donations every 12 weeks (♀)
    - deferral if Hb < 13,5 mg/dL (♂), < 12,5 mg/dL (♀)
  - 237 drop outs (45%)
Iron supplementation in blood donors (1) serum ferritin

![Diagram showing ferritin levels in males and females with different iron supplementations.](image)
Iron supplementation in blood donors (1)

$\log(TfR/F)$

**deferral (Hb):**

- Males: $n = 3$ vs. $2$ vs. $9$; $p = 0.022$
- Females: $n = 1$ vs. $2$ vs. $10$; $p = 0.001$
Iron supplementation in blood donors (1) 
frequency of adverse effects

<table>
<thead>
<tr>
<th>adverse effect</th>
<th>40 mg iron</th>
<th>20 mg iron</th>
<th>Placebo only</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal complaints</td>
<td>9.4 %</td>
<td>10.7 %</td>
<td>8.4 %</td>
</tr>
<tr>
<td>signs of anemia</td>
<td>1.7 %</td>
<td>1.1 %</td>
<td>2.2 %</td>
</tr>
<tr>
<td>other symptoms</td>
<td>13.3 %</td>
<td>6.2 %</td>
<td>8.4 %</td>
</tr>
</tbody>
</table>

No significant difference between groups
Iron supplementation in blood donors (2)  
study design

• open study:  
  165 regular blood donors (83 ♂, 82 ♀)  
  – whole blood donation on day 0  
    • follow-up after two months (♂)  
    • follow-up after three months (♀)  
  – iron supplementation:  
    • 20 mg per day of elemental iron (ferrous-gluconate) for  
      30 days (total dose 600 mg)  
    • ascorbic acid and other vitamins  
  – 66 drop outs (40%)
Iron supplementation in blood donors (2)
Increasing donation frequency
study design

- placebo-controlled double-blind study: 260 participants (247 ♂, 3 ♀)
  - regular blood donors, body weight ≥ 68 kg, Hb ≥ 14,5 g/dl
  - 2-unit RBC apheresis at intervals of 8 - 10 weeks
    - Haemonetics MCS+, protocol SDR
  - iron supplementation: daily 100 mg of iron(II) or placebo, respectively
Increasing donation frequency
study design

- Group A: iron from visit 0-3, placebo from visit 3-6,
  Group B: placebo from visit 0-3, iron from visit 3-6
- Deferral if Hb < 14 g/dl
- 66 dropouts (25%)
Increasing donation frequency
serum ferritin

deferral (Hb): 18% of 1519 visits (placebo: 186, iron: 82; p<0.001)
Increasing donation frequency
frequency of adverse effects

<table>
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<th>Placebo treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal complaints</td>
<td>8,7%</td>
<td>5,2%</td>
</tr>
<tr>
<td>signs of anemia</td>
<td>3,9%</td>
<td>3,9%</td>
</tr>
<tr>
<td>other symptoms</td>
<td>5,7%</td>
<td>8,2%</td>
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</table>

No significant difference between groups
Conclusion

• 20 mg iron for 30 days (total dose 600 mg) adequately compensates for iron loss from whole blood donation
• 100 mg iron daily compensates a substantial increase in donation frequency
• tolerance of iron supplementation was good
• limited supplementation (study 2) less likely to obscure underlying disease
• the form of iron used (study 1,2) meets the European Community criteria for dietary foods for special medical purposes
Thank you