

## Laboratory and Genetic Assessment of Iron Deficiency in Blood Donors

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#### **KEYWORDS**

- Blood donation Iron deficiency Ferritin Soluble transferrin receptor
- Reticulocyte hemoglobin content Hypochromic mature red blood cells
- Hereditary hemochromatosis (HFE) TMPRSS6

#### **KEY POINTS**

- Iron depletion is common in blood donors, especially women and frequent donors.
- Hemoglobin level is useful to detect anemia but has limited value in assessing blood donor iron status.
- Red blood cell indices, such the percentage of hypochromic mature RBC and reticulocyte hemoglobin content can improve the assessment of iron status over hemoglobin alone.
- Current studies suggest that measurement of ferritin at a level of 26 to 30 ng/mL optimally identifies donors who are iron depleted.
- Genetic assessment of iron pathways may reveal new approaches for selecting individuals who are more or less able to donate blood on a regular basis.

#### **BLOOD DONORS AND IRON DEPLETION**

Blood donors and the red blood cells (RBCs) they provide serve as a vital link in the delivery of health care worldwide. More than 9 million volunteer blood donors donate each year in the United States.<sup>1</sup> Nearly 70% are repeat donors, many of whom become iron deficient as a result of regular blood donation.<sup>2,3</sup> Moreover, nearly 7% of presenting donors are deferred from donating because they cannot meet the minimum hemoglobin standard of 12.5 g/dL obtained by finger-stick testing. The US Food and Drug Administration (FDA) defines this as the minimum hemoglobin value in both men and women to determine donor eligibility, but no requirement currently exists for determining iron levels. Low hemoglobin, a late consequence of iron deficiency,

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Abbreviations	
AIC	Abcent iron stores
AIS	Absent non stores
AUC	Area under the curve
CHCIVIM	Cellular nemoglobin concentration of mature RBC
CHr	Reticulocyte nemoglobin content
FDA	Food and Drug Administration
GWAS	Genome-wide association studies
HYPOm	Hypochromic mature red blood cells
HYPOr	Hypochromic reticulocyte red blood cells
IDA	Iron-deficiency anemia
IDE	Iron-deficient erythropoiesis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
rHuEpo	recombinant human erythropoietin
R/F ratio	sTfR/ferritin ratio
RBC	Red blood cell
RISE group	Retrovirus Epidemiology and Donor Evaluation Study-II Iron Status Evaluation group
ROC	Receiver operating characteristic
SNP	Single nucleotide polymorphism
sTfR	Serum soluble transferrin receptor
TIBC	Total iron-binding capacity
ZPP	Zinc protoporphyrin

represents the largest category of blood donor deferral and occurs more frequently in women. In addition, women are 3 times more likely to be iron deficient than men.<sup>4</sup> Even in the absence of anemia, iron depletion has been associated with several conditions arising from the key role iron plays in the central nervous system and neuromuscular function,<sup>5</sup> including fatigue,<sup>6</sup> decreased exercise capacity,<sup>7</sup> neurocognitive changes,<sup>8</sup> pica (the compulsive ingestion of non-nutritive substances, such as ice), and restless legs syndrome.<sup>9,10</sup>

Overall, 35% of the blood donor population in the United States is estimated to be iron deficient.<sup>4</sup> The large number of affected blood donors and recognition of the potential health consequences has prompted the main blood banking organization, the American Association of Blood Banks, to recommend that measures be adopted to identify and to prevent iron deficiency in all or in selected high-risk individuals. As a result, blood collection centers worldwide are examining potential strategies to manage donor iron loss, including changes in acceptable hemoglobin level, donation interval, donation frequency, testing of iron status, and iron supplementation. This review considers the relative merits of different laboratory and genetic tests to assess the iron status of blood donors and their suitability as screening tests for blood donation.

### BRIEF REVIEW OF IRON PHYSIOLOGY IN MEN AND WOMEN

Iron is an essential element in many physiologic processes. In association with heme, it participates in the reversible binding of oxygen by RBCs and is also a key constituent in the myoglobin of muscle and mitochondrial cytochromes. Nonheme iron plays a key role in the activity of many enzymatic reactions. Iron may also be toxic when present in excess; absorption is tightly regulated because there is no active mechanism for excretion. Dietary iron is absorbed in the proximal small intestine. Iron from animal

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