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Iron Status of Blood Donors

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Abstract

Purpose of review: This review examines recent research on the prevalence and importance of iron deficiency in blood donors, and on efforts to mitigate it.

Recent findings: Pre-menopausal females, teenagers, and high-frequency donors are at highest risk for donation-induced iron deficiency, in both high- and low-resource settings. The physiology relating iron stores to hemoglobin levels and low hemoglobin deferral is well elucidated in blood donor populations, yet the clinical effects attributable to iron loss in the absence of anemia are challenging to identify. Expanded adoption of ferritin testing is improving donor management but may cause decreases in the blood supply from temporary donor loss. The potential for personalized donor management is emerging with development of computational models that predict individual inter-donation intervals that aim to optimize blood collected from each donor while minimizing low hemoglobin deferrals.

Summary: Measures to reduce iron deficiency are available that can be deployed on a standardized or, increasingly, personalized basis. Blood centers, regulators, and donors should continue to evaluate different approaches for addressing this problem, to obtain a balanced approach that is optimal for maintaining adequate collections while safeguarding donor health.

Keywords

blood donation; iron deficiency; hemoglobin; ferritin; personalized transfusion medicine

Introduction

Hemoglobin measurement protects blood donors, by deferring those with low hemoglobin, and helps the recipient by ensuring adequate hemoglobin content in transfused red blood cells (RBCs). Approximately 10% of donors are deferred for low hemoglobin [1]. Blood donation removes ~525 mL of blood containing ~250 mg iron [2]. However, screening

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for iron deficiency (ID) is not routinely performed, and low hemoglobin typically occurs following depletion of iron stores. Consequently, donors of both sexes become iron deficient [3]. The symptoms of ID are substantial, including fatigue[4,5], pica [6–9], and restless leg syndrome [6,7,9–11]. Here, we review recent advances in the understanding of ID in blood donors, and how it is successfully mitigated.

Prevalence of ID in Blood Donors

It is long-established that repeated blood donation depletes iron stores [12,13], yet most blood centers measure iron stores intermittently, in select populations, or not at all [14,15]. Hence, systematically collected operational data are unavailable to characterize donor iron status. Instead, estimates are often based on cross-sectional snapshots, research models, or other less than systematic data. Nevertheless, recent studies offer generally reliable estimates of the prevalence of ID in donors worldwide.

Investigators in the United States (US) and Canada found ferritin <12 ng/mL in ~15% of donors and ferritin <26 in ~38% when the hemoglobin cut-off was 12.5 g/dL and donation was allowed every 8 weeks for both sexes [16–18]. An Australian study found ferritin <15 ng/mL in 14% of donors [19], and one from Iceland found ferritin <15 ng/mL in ~25% of female and 9% of male donors [20]. Emerging evidence from lower-resource countries substantiates concern for iron depletion in their blood donor populations (Table 1). Studies from Africa and India confirm high prevalence of ID [21,22], and one from Ghana shows that 5 months is insufficient for 77% of donors to return to pre-donation ferritin levels [23]. A study from South Africa, which used additional biomarkers for iron besides ferritin, indicates a degree of caution in estimating ID against a background where inflammation or other factors might artifactually raise ferritin levels [21]. This finding mirrors results in pediatric populations in Africa where the estimated prevalence of ID increased from 34% based on ferritin alone to 52% following correction for inflammation and infection [24]. Hence, ferritin-based estimates may underestimate the prevalence of low iron in donors at some locales.

Recent studies examined iron status relating to apheresis collection of platelets, plasma, or double red cells. A US study of male plateletpheresis donors with low-normal hemoglobin found high prevalence of ID and a clear dose-response association with plateletpheresis donation count [25]. In contrast, a study of plasma donors found that ID was rare and not more common in high frequency donors [26]. Recent findings indicating that with 24-week intervals between double red cell donations young men maintain stable hemoglobin and ferritin over several years [27] may be attributable to stringent minimum weight and hemoglobin eligibility criteria.

Demographic factors contribute to iron status in new and established blood donors. The greater risk for ID in female compared to male donors is well characterized and confirmed in recent studies. Reporting ID by sex, Simon (23 vs 8%) [13], Goldman (24 vs 12%) [18], and Fillet (19 vs 6%) [28] all documented a 2- to 3-fold higher prevalence among female donors. While unadjusted figures do not account for potential confounders, the REDS-II

RISE and REDS-III RBC Omics studies reported adjusted odds for ferritin <12 ng/mL as 3-fold greater for females than males [3,16].

Differences in risk for ID across age groups requires careful assessment, given differences in donation patterns and other causal factors associated with iron levels. In the US, the positive correlation between age and prevalence of ID in males may be accounted for by higher donation frequency in older male donors and secondary risk factors, including proton pump inhibitor medications and testosterone therapy [16,29]. In females, a declining risk following childbearing years is firmly documented in the US [3,16,30], Denmark [31], France [28], Iceland [20], and Finland [32].

The risk for ID in high school donors has drawn considerable scrutiny in the US as the proportion of the blood supply sourced from teenage donors increased in recent years [33]. An operational ferritin testing program for donors aged 16–18-years-old showed that, contrary to adult donors, a small proportion (1.7%) of young male donors have ferritin <12 ng/mL and low ferritin is especially prevalent in females [34]. The REDS-III CHILL study showed in regression models that teenage donors had adjusted odds for ID 2- to 5-times greater than adult donors, depending on the ferritin level and age group [35]. Another study reported that <50% of teenage donors with low ferritin recovered to adequate ferritin levels in 12 months following donation [36]. Several blood collectors in the US, accounting for about 70% of the blood supply, now routinely test ferritin for 16 to 18 year-old donors, applying a precautionary approach pending clear demonstration of harm in this population [37].

Impact of ID on blood donor health

Donation-associated ID in females of childbearing age is a longstanding concern [38]. Recent studies utilized public datasets to evaluate potential risks from pregnancies in donors with ID. In Canada, Germain reported no association between female donation frequency prior to pregnancy and subsequent low birth weight, preterm delivery, or stillbirth [39]. Another Canadian study found no association between blood donation and birth weight [40]. A Scandinavian study found modestly lower birth weight in infants born to former donors, but the risk for low birth weight was not increased [41].

The attention on teenager donors is driven primarily by concern about the relationship between ID and altered cognitive function. Iron is essential for neurological development, and a causal association between low iron and cognitive outcomes is well documented in infants and young children [42]. Suggestive but not conclusive studies point to the potential for adverse outcomes in adults, particularly in young women [37]. In the United Kingdom, the INTERVAL study assessed cognitive function in adults at study onset and conclusion. Although large differences in hemoglobin and ferritin levels were found by donation frequency, none of five cognitive function assessments was associated with iron status [43]. Danish investigators compared scholastic outcomes of children born to female donors to those of non-donors. While finding a notable “healthy donor effect”, there was no difference in academic achievement between the two groups [44]. In the US, a cross-sectional analysis

found no association between cognitive performance and iron status or blood donation in young women [45].

Pica, the compulsive craving, and ingestion of non-nutritive substances is associated with iron depletion in general [46] and blood donor [6,7] populations. Pica was present in 2.2% of a mostly representative US donor population and associated with low ferritin as well as restless leg syndrome (RLS) [9]. In several donor studies an association between iron and RLS was not found [6,7,47], but one recent study reported improvements in RLS, sleep, and fatigue following use of exogenous iron [48]. An association with proton pump inhibitor medications and RLS was recently reported, even after controlling for iron status, emphasizing its multi-factorial etiology [49].

Fatigue, decreased exercise endurance, and “quality of life” conditions have been examined in donors given associations with low iron and low hemoglobin. The INTERVAL study reported a higher frequency of tiredness and lower ferritin in more frequent donors, but findings were inconsistent across survey instruments and did not disentangle effects relating to hemoglobin from those relating to iron [43]. Analogous findings were reported from the US STRIDE study, which found sizable changes in both self-reported fatigue and donor iron status, but that these changes did not correlate at the individual level [50]. Similar conflicting findings were reported by Pachikian, in a blinded trial of young male athletes including one providing “sham” blood donations. They found that supplemental iron of 20 to 80mg daily did not markedly alter post-donation ferritin recovery, but it did support more robust physiological performance, including VO2 max [51]. The methodological challenges of documenting iron-related adverse events in donors are shown by a post-donation survey conducted in Germany [52]. The questionnaire completed by over 8,000 donors found that 27% reported an adverse reaction (AR) at their last donation, and 64% occurred after leaving the blood establishment. The authors reported 7% of ARs were attributable to ID-related factors, but it is not evident they distinguished iron- vs hemoglobin-related effects. Illustrating the methodological challenges detailed by Spencer [50], Finnish investigators reported an association between low ferritin and worsening health, but with substantial loss to follow up and significant risk of selection bias [53]. Iron and hemoglobin affect not just donor health but also retention. Karki reported a lower rate of successful return amongst Australian donors who received an iron-related deferral [54].

Physiology of Ferritin and hemoglobin in blood donors

Reinforcing previous work, the Danish Blood Donor Study reported that gender, number of previous donations, time since last donation, and menstrual status are the best predictors of donor ID, while the strongest predictors of low hemoglobin deferral are ferritin and iron supplement use [55]. These conclusions are supported by recent reports that expand our understanding of hemoglobin and iron physiology. The BEST Collaborative performed a survey of low hemoglobin deferral at 38 blood services worldwide. Low hemoglobin deferral rates varied over 30-fold between different sites. Notably, the variation was linked to the local inter-donation intervals rather than local hemoglobin cut-offs [56]. Timmer examined the effect of dietary iron on hemoglobin in 2,323 Dutch donors finding that hemoglobin increased 0.16 mmol/L for each additional gram of heme iron intake and

decreased 0.014 mmol/L for each additional gram of non-heme iron intake [57]. However, a study of 2,000 Finish donors found that donation frequency was most important determinant of donor iron stores, far more important than red meat consumption or iron supplementation [58], a finding consistent with earlier studies showing that full recovery of iron stores following blood donation takes over 100 days in those taking daily iron supplements and over 180 days in non-supplemented donors [59–61].

Whole blood donation removes ~10% of the donor's blood volume, putting stress on iron metabolism and erythropoiesis. This makes donors a unique population for studies of human hemoglobin and iron metabolism [60]. To identify physiologically-based ferritin thresholds for ID, Addo analyzed 5,442 20- to 49-year-old female donors in the US [62]. They found a plasma ferritin threshold of 25.4 ng/mL corresponding with the soluble transferrin receptor (sTfR) minimum plateau and a hemoglobin plateau. This suggests plasma ferritin of 25.4 ng/mL represents a physiological point below which there is exhaustion of available iron stores signaled by rising sTfR and declining hemoglobin. Consistently, a study of 5,056 Dutch donors found that those with plasma ferritin <15 ng/mL had 21.8 (male), 10.1 (premenopausal female), or 11.7 (postmenopausal woman) higher odds for low hemoglobin deferral at a subsequent donation attempt when compared to donors with plasma ferritin >30 ng/mL [63]. REDS-III investigators examined recovery of erythropoietin, reticulocytes, total body iron, RBC iron, storage iron, and hepcidin using samples collected from 193 subjects at baseline donation and during 24-week follow-up. Donors were randomized to receive 37.5 mg daily oral iron or no iron over the study period. Iron supplements had minimal impact on recovery of RBC iron when baseline plasma ferritin was ≥50 ng/mL but had substantial impact when <50 ng/mL. Interestingly, iron absorbed immediately following donation replaced iron stores and RBC iron when baseline ferritin was <12 ng/mL but primarily replaced RBC iron when ferritin was ≥12 ng/mL. Further, reticulocytes increased ~100 days following donation. This represented new RBC synthesis to replace those produced following donation and approaching the end of their 120-day life span [60]. Thus, physiologic responses to blood donation occur well beyond the 56-day inter-donation interval that is the standard in several countries.

Blood donors also are a unique population to identify genetic variants that impact hemoglobin and iron stores. Earlier work found that *HFE* mutations do not alter the rate of hemoglobin and ferritin change that occur with multiple donations, and the prevalence of these mutations is not increased in high intensity donors [64]. However, high intensity blood donors have low hemoglobin deferrals less often than other donors [65], suggesting genetic variants exist that alter the rate of dietary iron absorption following blood donation. Studies of Danish donors found genetic variants in *HFE* and *TMPRSS6* may protect from low hemoglobin or low iron stores [66]. A REDS-III study measured the *TMPRSS6* A736V variant in the longitudinal REDS-II RISE study and found it is associated with a rapid drop in hemoglobin and ferritin in first-time female donors following repeated donation [67]. However, in an unbiased assessment of genetic variability in the cross-sectional REDS-III RBC-Omics study, the protective *TMPRSS6* genotype was not enriched among high-intensity donors. Further, a genome-wide association analysis did not identify differences in genotype between first-time and high-intensity donors [67]. Thus, it appears that behaviors,

such as use of iron supplements, are more important than underlying genetics in allowing donors to repeatedly donate blood without experiencing low hemoglobin deferral [67].

Blood collection organizations are obligated to educate donors about donation-associated ID and its prevention. Successful mitigation strategies will benefit the donor by improving their health, and will benefit the donor and the blood collection organization by minimizing the loss of time and financial resources associated with low hemoglobin deferrals. Knowledge of demographic and genetic risks for ID and low hemoglobin deferral, along with hemoglobin and iron recovery profiles and how they are impacted by baseline ferritin, have stimulated interest in prediction of individualized donation intervals based on estimated recovery trajectories for each donor. Development of personalized donation intervals requires a balance between the maximal units collected that occur with shorter intervals and low hemoglobin deferrals that decrease with longer intervals. Three recent papers developed computational techniques to determine personal inter-donation intervals [68–70]. They found considerable variability among donors, justifying this approach. Continued work is needed to optimize computational strategies and to define necessary demographic and biochemical data needed from donors.

Iron supplementation and other mitigation approaches

Iron supplementation, ferritin measurement, and altered donation intervals represent successful approaches for mitigation of ID in donors. Blood collection organizations are challenged with making these operationally effective without negatively impacting blood availability. Some donors recognize the benefits of taking iron, and ~50% of high intensity donors do so [71]. However, only 21% of an unselected group of 53,989 donors in the US reported taking iron [72]. France studied 1,533 donors in the US finding that providing information about risk for iron depletion and behaviors to mitigate risk, improved post-donation iron use without impact on donor retention. However, ~45% of the educated donors still did not take iron [73]. Investigators have examined extending the inter-donation interval based on the donor’s ferritin level. A program in the Netherlands extends the interval to 6 or 12 months if ferritin is below 15 or 30 ng/mL, respectively [74,75]. This policy effectively mitigates ferritin below 15 ng/mL when returning following deferral. Overall, the deferred donors made fewer donations, but also had fewer low hemoglobin deferrals resulting in improved donor retention. However, the program decreased the blood supply, requiring collection of more units from non-deferred donors, which puts those donors at increased risk for low ferritin, or recruitment of new donors. The impact of ferritin testing on whole blood collection was modeled by Blake using Canadian Blood Services data [76]. The model predicts 3.1% decrease in donations if intervals were extended to 6 months when ferritin is <26 ng/mL. The authors emphasized that ferritin testing programs need to be coupled with educational programs to encourage return following deferral. Limitations of these models are that they did not include the impact of fewer low hemoglobin deferrals and did not incorporate use of iron supplements by donors, which substantially enhance recovery of ferritin following donation.

Conclusion

Blood donation places considerable stress on donor iron stores placing them at risk for ID and ID anemia. Improved communication of the importance of iron for recovery following blood donation is needed, as well as development of programs that mitigate donor ID without impacting the blood supply.

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Key Points

- Intermediate and advanced iron deficiency are common in blood donors in high- and low-resource countries.
- Premenopausal women, young donors, and high-frequency donors are at greatest risk of donation-induced iron deficiency.
- Although studies assessing serious outcomes relating to donation-associated iron loss (alterations of cognitive function or adverse pregnancy outcomes) have been negative to date, few studies have been conducted and a precautionary approach is appropriate for vulnerable donors. Pica, restless legs syndrome, fatigue and other quality of life conditions continue to be studied.
- Ferritin testing is reducing reliance on hemoglobin as an indicator of iron status in some donor populations. Iron-depleted donors are increasingly provided information about iron deficiency that empowers them to take measures to protect their health and wellbeing.
- Supplemental iron mitigates iron deficiency, but distribution of iron by blood collecting organizations is not commonly practiced. The opportunity to personalize donor management is beginning to take shape.

Table 1:

Selected studies on the prevalence of iron depletion in blood donors

Study Site	Study Population & Design	Key findings
Ghana [23]	164 donors, paired analysis of prospective cohort 287 donors, cross-sectional study	• After 5 months post-donation, 77% of donors (94% male) had not returned to pre-donation ferritin levels • Prevalence of iron depletion (ferritin <15 ng/mL) was 10% and iron deficiency erythropoiesis (ferritin 15–30 ng/mL) was 21% after 5 months • Use of supplemental iron was low (11%), and prevalence of ferritin <15 ng/mL was 27%
South Africa [21]	4412 adult donors, cross-sectional study	• Iron depletion was high in female (16% with ferritin <12 ng/mL) and male donors (19% with ferritin <20 ng/mL) • Distributions of TSAT suggest a prevalence of ID considerably higher than ferritin-based estimation
India [22]	374 donors, cross-sectional study	• Prevalence of ferritin <15 ng/mL was 16%, and another 10% had ferritin 15–30 ng/mL
Iceland [20]	32,910 donors, 85,370 ferritin measurements over 23 years	• Ferritin <15 ng/mL was found in 25% of female donors and from 16% of donations from females; in males the corresponding figures were 9% and 5%. • Iron-deficiency anemia was found in 1.6% of donations from females and 0.4% of those from males.
France [28]	11,258 donors, cross-sectional study	• Prevalence of ferritin <26 ng/mL of 29% and <15 ng/mL of 13%.
Finland [32]	2,200 donors, prospective cohort	• Ferritin <15 ng/mL was found in 6% of men, 10.6% of post-menopausal women, and 20.6% of pre-menopausal women. • Donation frequency explained much more variance in ferritin levels than demographic, behavioral, or dietary factors.