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Blood donor iron status: are we bleeding them dry?

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Abstract

Purpose of review—To examine the recent research on the prevalence, determinants and importance of low iron in blood donors, and on the efforts to reduce or prevent iron depletion in donor populations.

Recent findings—Female donors, especially younger women, are at highest risk for donation-induced low iron, but menopausal women and high-frequency donors of both sexes also face considerable risk for iron depletion. Predonation screening for hemoglobin contributes little information on donor iron status. Consumption of supplemental iron is helpful in preventing or reversing low iron, and waiting longer between donations also facilitates the recovery of the iron lost through donation.

Summary—Although the impact of phlebotomy-related iron depletion on donor health requires better documentation, measures are available now that can be deployed on a targeted or standardized basis. Blood centers, regulators, and donors should continue to evaluate different approaches for addressing this problem, with the likely outcome that no single measure is optimal for maintaining adequate collections while safeguarding donor health.

Keywords

blood donation; iron depletion; iron replacement

INTRODUCTION

Despite the growing efforts to optimize patient care with evidence-based blood transfusion strategies [1,2], the use of blood components in the USA shows a long-term trend of growing demand [3]. The increased support for more restrictive transfusion practices and recent moderation in usage [4] are likely to be counterbalanced by the challenges of an aging population [5]. This demographic imperative operates on two levels, with a diminishing supply of younger healthy donors and an increasing share of the elderly population whose utilization rates are multiples of those in younger age groups [6]. The result is a continuing reliance on repeat blood donors for up to 70% of blood supplies [4], and the attendant risk that blood donor iron status fails to keep pace with phlebotomy-related losses.

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Conflicts of interest

None.

The negative association between blood donation and donor iron stores was convincingly shown more than 3 decades ago, with women of child-bearing age and high-frequency blood donors at particularly high risk for reduced iron stores, defined as plasma ferritin measuring less than 12 ng/ml [7,8]. In the recent years, several factors have increased the opportunity for more intensive blood donation. Many blood centers have increased the use of double red cell collections by apheresis technology, they have increased container volume for whole-blood collections from 450 to 500 ml, and they have reduced the minimum hemoglobin (Hb) for male donors from 13.5 to 12.5 g/dl, the same cutoff used for female donors. The U.S. government defines a minimum Hb or hematocrit level to qualify a blood donor, but no requirement exists for the screening of donor iron levels. In practice, Hb levels are often considered an indirect proxy of donor iron status.

Regulatory attention on appropriate donor screening for Hb and maintenance of iron stores has grown in the last several years. Following a proposed rule by the U.S. Food and Drug Administration in November 2007 [9] that requested comment on lowering the Hb threshold for female donors to 12.0 g/dl, maintaining the Hb requirement for male donors at 12.5 g/dl, and increasing the minimum interdonation interval beyond the current length of 8 weeks, these issues have been reviewed at numerous public forums sponsored by the U.S. regulatory authorities. These discussions have included results from multiple large, well designed research studies addressing different aspects of donation-induced iron losses. This review summarizes the recent data on the prevalence, determinants and impact of low iron in blood donors, and on the mitigation strategies to reduce the problem.

PREVALENCE AND DETERMINANTS OF LOW IRON IN BLOOD DONORS

Establishing the iron status of a blood donor population as a whole is a complex undertaking, given the dynamic nature of the phenomena under observation. Whether the level of analysis is a country or simply a given blood center, the population of donors is in constant flux: new donors get recruited, some established donors discontinue blood donation for multiple reasons, whereas others might have highly variable donation patterns. A cross-sectional analysis of blood donors, such as the early studies of Finch and Simon [7,8], provide simply a snapshot of a given point in time. Well constructed, longitudinal studies offer the opportunity to more rigorously determine the frequency and causes of low iron in blood donors. In the Retrovirus Epidemiology and Donor Evaluation Study (REDS-II) RISE study (REDS-II Donor Iron Status Evaluation), Cable *et al.* [10^{©©}] recruited two distinct donor groups to study the impact of blood donation and other factors on donor iron status: those who had not previously donated (first-time donors) or not within the prior 2 years (reactivated donors), and those who were frequent repeat donors (2+ or 3+ donations in prior year for female and male donors, respectively). At enrollment ($n = 2425$), female donors of childbearing age were approximately 3–7 times more likely to have iron depletion, defined as absent iron stores (AIS), or serum ferritin less than 12ng/ml than menopausal women or male donors. The prevalence of AIS ranged from 0% in first-time male donors to 27% in frequent female donors. Iron-deficient erythropoiesis (IDE), a composite measure of ferritin and soluble transferrin receptor derived from the values of first-time male donors (unaffected by recent blood loss), was found in nearly half of frequent male donors and two out of three frequent female donors. In statistical models controlling for demographic, behavioral, and

other factors, donation intensity stood out as the most important predictor by far, with those donating 10 times or more over the prior 2 years 19 times more likely to have AIS than first-time donors and 50 times more likely to have IDE, an intermediate degree of iron depletion. The importance of donation frequency as a contributor to iron depletion in blood donors was underscored at the end of 15 months or more follow-up ($n = 1334$), by which time the prevalence of AIS in the first-time/reactivated donor cohort had tripled in women (6.6 to 20%) and risen from 0 to 8% in men; similar dynamics obtained for IDE albeit at much higher frequency [11[©]]. Conversely, the overall prevalence of AIS and IDE remained steady within frequent repeat donor cohorts of each sex. Longer intervals between donations (up to 13 weeks) were associated with lower risk for AIS, as was consumption of iron supplements or multivitamins containing iron.

Whereas the RISE study enrolled only individuals eligible for donation, the prevalence of low iron in donors receiving deferral for low Hb was estimated in another longitudinal study carried out by Bryant *et al.* [12[©]] at the U.S. National Institutes of Health. The Iron Replacement or Not (IRON) study was designed to assess the efficacy of iron replacement following a successful donation, with investigators applying sex-specific ranges of serum ferritin to define iron depletion or deficiency. Of men deferred for low Hb, 61% had either iron depletion (ferritin 18–29 ng/ml) or iron deficiency (ferritin <18 ng/ml) and 53% of women were classified as having iron depletion (ferritin 9–19 ng/ml) or iron deficiency (ferritin <9 ng/ml). Of a ‘control’ group of donors accepted for donation, 39% of men and women alike were classified into one of the two low-iron outcomes, buttressing the RISE study’s indications of high prevalence of low iron in U.S. blood donors.

In other jurisdictions, the same phenomenon is observed despite the donation guidelines that are more restrictive in terms of allowed frequency of donation, whether defined as minimum intervals between donations or a maximum number of annual donations allowed. In a large study ($n = 5280$) of Dutch donors accepted for donation, Baart *et al.* [13] estimated that 6.9% of male donors and 9.8% of female donors had subclinical iron deficiency as defined by zinc protoporphyrin (ZPP) levels of at least 100 $\mu\text{mol/mol}$ heme. Other assays, including ferritin, transferrin saturation, soluble transferrin receptor, and hepcidin, suggested a prevalence of iron deficiency ranging from roughly 5 to 25% in male and female donors alike. This finding underscores the importance of ensuring that comparisons of iron deficiency across the studies are based on similar laboratory parameters.

IDENTIFYING LOW IRON IN BLOOD DONORS AND LIMITED VALUE OF HEMOGLOBIN MEASUREMENTS

Simon’s [8] article showed more than 30 years ago that cumulative lifetime donations were strongly correlated with ferritin levels in cross-sectional analysis, but virtually unrelated to Hb levels. Nonetheless, donors, phlebotomists, recruiters, and others often use the terms ‘hemoglobin’ and ‘iron’ interchangeably or equate ‘low iron’ to ‘anemic’. The RISE study presents both epidemiological and laboratory evidence that Hb serves as a poor proxy for iron status. In longitudinal models, the strongest predictor of AIS in donors is donation frequency over the prior 2 years; yet, this same variable is unrelated to risk for deferral for

low Hb [11[©]]. Other analyses of REDS-II donation data [14] (B. Spencer in preparation) indicate ‘protective’ effects of high donation intensity against Hb deferral. Though the effect captured is more likely behavioral than biological –an ability of frequent donors to identify a rhythm at which they can donate without failing the Hb screening – the disparate association of donation frequency with outcomes relating to iron status and Hb is notable. The RISE study also shows that the ability of Hb samples drawn from fingerstick to reflect venous Hb levels varies by sex and by donor iron status [15[©]]. Whereas fingerstick Hb were generally on par with venous Hb in iron-replete male donors, fingerstick Hb values overestimated venous values by 0.5–0.8 g/dl in women and up to 1.0 g/dl in male or female donors with AIS. The RISE study contrasts with a large study ($n = 36\,258$) from the Irish Blood Transfusion Service that showed larger gaps between venous and fingerstick measurements for men (1.07 g/dl) than for women (0.67 g/dl) and greater differences in winter compared with summer months [16]. Notably, the association was reversed with venous Hb values being higher than those from fingerstick samples. The results from these two studies suggests caution against interpreting point-of-care Hb tests as reflecting absolute precision, as opposed to reasonable approximations of a donor’s hematological status.

Concern for appropriate Hb screening of donors was indicated by the Food and Drug Administration (FDA) proposed rules in 2007, and a Health and Human Services advisory committee endorsed sex-appropriate Hb acceptance values the following year. The Advisory Committee for Blood Safety and Availability noted that a uniform cutoff of 12.5 g/dl allowed ‘anemic’ men to donate while excluding normal women [17], conclusions supported by the analyses of large population-based datasets [18]. Although the RISE study found a high prevalence of iron deficiency (77%) in Hb-deferred donors [11[©]], other recent analyses show generally poor prognostic value of ferritin in predicting anemia [19[©]] and of venous Hb values in predicting low ferritin [20]. The clear lesson from the accumulated evidence is that donor Hb is a lagging indicator and highly imperfect proxy for donor iron status, and that where the latter is of interest it should be directly measured.

IMPACT OF LOW IRON ON DONOR HEALTH

The evidence available today demonstrates unequivocally that blood donation contributes to iron depletion in some blood donors. Recent studies have helped delineate the relative importance of various determinants of iron depletion, but the clinical correlates are less clear. Reported consequences of low iron include fatigue, cognitive deficits, pica, and restless legs syndrome (RLS) [21], but few studies have attempted to evaluate these in blood donors.

The IRON study by Bryant [22[©]] inquired into the symptoms of RLS and pica, finding both conditions more common in donors with iron depletion or iron deficiency than in iron-replete donors. Pica was reported by 11% of donors with low iron compared to 4% of iron-replete donors, though the association with low iron was restricted to women. RLS was reported by 16% of donors with low iron and 11% of iron-replete donors. Both pica and RLS were reversible with the administration of supplemental iron, pica much more quickly than RLS.

Similar findings were found by Spencer *et al.* [23[©]] from the RISE cohort, albeit assessed only once at the study's conclusion. Pica was reported by 6% of donors completing the study ($n = 1334$), and in multivariate models was eight times more likely in women with AIS (ferritin <12 ng/ml) than in iron-replete women. Probable RLS (9%) or possible RLS (20%) were reported by more donors than was pica, but there was no statistical association with measured ferritin levels.

Whether phlebotomy-related iron loss causes clinically meaningful fatigue is a question that has been little studied. In nondonor premenopausal women, two randomized, placebo-controlled trials have demonstrated the efficacy of oral [24] and intravenous [25] iron formulations in improving the fatigue levels in nonanemic individuals with low iron. By analogy, one might expect to find similar results in nonanemic women accepted to donate who lose a significant amount of their iron stores in a single donation, but the results thus far are mixed. In a study carried out at the Swiss Red Cross, Waldvogel *et al.* [26[©]] found that a 4-week course of oral iron following donation did not improve fatigue, and furthermore results did not support the conclusion that donation-induced fatigue was a common phenomenon. In contrast, a case-control study conducted by other Swiss Red Cross investigators concluded that 16 weeks of iron substitution in nonanemic donors significantly reduced fatigue, by far the most common symptom (70% of treatment individuals) reported at the study inception [27]. In the Netherlands, Van Dongen *et al.* [28[©]] estimated the onset of fatigue in less than 2% of first-time blood donors ($n = 1278$), though return rates in men reporting fatigue were 50% lower. Early returns from a U.S.-based cohort of frequent donors indicate relatively low prevalence ($<10\%$) of clinically significant fatigue, and the association with iron status at enrollment is not statistically significant [29].

OPTIONS FOR PROTECTING AGAINST LOW IRON IN BLOOD DONORS

Defining the magnitude of the problem and debating solutions has been the subject of multiple workshops and meetings sponsored by the regulatory authorities in the USA. From a 2001 workshop on iron balance in women of childbearing age [30] to a November 2011 workshop discussing Hb screening and iron status of blood donors (FDA Workshop on Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors), numerous strategies have received robust discussion. In 2011, a task force was charged by AABB (formerly the American Association of Blood Banks) with developing a donor Information sheet and an Association Bulletin to provide guidance to blood centers, which was released in September 2012 [31]. This Bulletin recommends one or more of the following measures for all or at least selected high-risk donors to identify and to prevent iron deficiency in blood donors:

1. Measurement of serum or plasma ferritin.
2. Replacement iron following donation, either provided directly by the blood center or obtained over-the-counter by the donor.
3. Lengthening the interdonation interval or restricting annual whole blood or apheresis red cell donations.

Further, the Bulletin recommends tracking of the measures undertaken to allow for efficacy assessments. The importance of better donor education is underscored by a recent study by Delaney *et al.* [32] who reviewed blood center management and blood donor understanding of low Hb deferrals. As much variability and confusion may exist regarding the discussion of anemia, less attention is paid to the donor iron stores. Otherwise, measure 2 in the foregoing list is that which has received greatest evaluation, and for which considerable evidence of success exists for improvement in the donor iron status. The RISE study indicated a protective effect of 30–40% for supplemental iron intake against IDE or AIS in blood donors, controlling for demographic factors and donation intensity [11[©]]. The IRON study, likewise, demonstrated acceptable levels of compliance and tolerability with 325-mg ferrous sulfate tablets for 60 days following donation, allowing for the donors with low Hb at enrollment to contribute 46% more donations compared with the general donor population in the blood center [12[©]]. As noted earlier, Pittori *et al.* [27] were successful in improving the donor ferritin levels with 16 weeks of oral iron, in addition to reversing the symptoms related to low iron. Another ongoing effort includes assessments of low (19 mg elemental iron) versus moderate (38 mg) doses of iron following donation in a randomized study [33]. The STRIDE study (Strategies to Reduce Iron Deficiency) also addresses the first recommendation from the AABB task force, namely testing of donor ferritin levels. Although they are being measured for all donors at all visits, one group is being provided their ferritin values by letter, with recommendations to consider extending their interdonation interval or to take supplemental iron if their ferritin values are low.

A similar effort has recently been implemented by the Blood Systems, Inc, which screens donors for ferritin if they are near the Hb cutoff and managing donor return according to the ferritin results [34[©]]. Early returns ($n = 226\,470$) indicate that 6% of male donor visits and 16% of female donor visits triggered ferritin testing, with roughly half that proportion deferred for 6 months for low ferritin. Multivariate modeling again highlights the importance of recent donation intensity for AIS over demographic or other factors (odds ratios of 22 for men with 10+ donations in the prior 2 years compared to those with none). Future analysis will determine donor compliance with the extended intervals and the success in allowing for better recovery of iron stores.

One important question, for blood centers and regulators alike, will be whether any mitigation measures should be applied uniformly to all blood donors or would the optimal approach be to adopt targeted methods. In its July 2010 Blood Products Advisory Committee (BPAC) Meeting [35], the Food and Drug Administration requested input on whether the Hb cutoff for women should be lowered to 12.0 g/dl, on whether the Hb cutoff for male donors should be raised above 12.5 g/dl, and on what the expected impact might be on blood availability where the minimum interdonation interval extended to 12 weeks for male donors and to 16 weeks for female donors. The committee unanimously agreed that although the lower Hb threshold for women was physiologically normal, the high prevalence of low iron in female donors presented from RISE raised concerns against expanding the eligibility for women with Hb levels on the low end of the normal range. Echoing the earlier recommendations from the Advisory Committee on Blood Safety and Availability (ACBSA) in 2008, the BPAC also endorsed raising male Hb cutoffs, without making a recommendation for a specific new threshold. Finally, the committee discussed without

making recommendations the potential effects of longer intervals, which preliminary data indicated might be sizable in terms of blood availability.

More rigorous analysis of this last point is beginning to emerge. One study based on a high-frequency donor population at Mayo Clinic estimated that combined losses might easily reach double digits for various combinations of Hb cutoffs and interdonation intervals under consideration [36[®]]. A simulation study combining REDS-II donation data and data from RISE points to a loss of blood components on the order of 8–13% with intervals lengthened to 12 or 16 weeks, respectively, for both sexes [37[®]]. The models predict that these measures would improve donor iron status, but that a large proportion of donors with AIS would remain iron deficient despite the extended period between donations.

The ongoing Hemoglobin and Iron Recovery (HEIRS) study, being carried out by the National Heart, Lung and Blood Institute (NHLBI)-sponsored Retrovirus Epidemiology and Donor Evaluation Study (REDS-III) program, lends support to the conclusions from the RISE simulations [38[®]]. HEIRS randomized 214 donors, stratified by sex, age, and predonation iron levels, to donate, and has assayed indicators of iron and hematological status from prior to the index donation and over the ensuing 24-week period. Aside from a clear acceleration in recovery for those randomized to take supplemental iron, another salient finding from the preliminary results is the considerable variability in recovery times for both Hb and iron lost in a single donation. Though some donors achieve recovery within an 8-week period, others require far more time. This finding, although preliminary, begs the question of whether donor qualification guidelines ought to be made universally more strict for all donors, or whether donors and blood centers would be better served with donation schedules tailored to reflect the interest and donation capacity of individuals or subgroups of donors.

CONCLUSION

Recent data confirm that blood donation is an important cause of iron depletion in blood donors. The correspondence is imperfect, with some individuals iron depleted prior to making their first donation and others able to donate frequently without ever exhausting their iron stores, much less progressing to iron-deficient anemia. The significant heterogeneity in donor return behavior, interest in and ability to take supplemental iron, and physiological factors argues for caution in devising new procedures for qualifying and managing donors. More targeted procedures, such as ferritin testing or iron replacement for high-risk donors (premenopausal women and frequent donors of both sexes), might be more successful in reducing low iron levels in blood donors with modest disruption to blood collections. Continuing analysis of ongoing efforts, including the HEIRS and STRIDE studies and the Blood Systems initiative, will inform efforts to maintain adequate blood collections while safeguarding donor health.

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KEY POINTS

- Intermediate to advanced iron depletion is common in blood donors.
- Women, especially younger women, and high-frequency donors are at greatest risk of donation-induced iron depletion. Waiting longer between donations and taking supplemental iron help protect against low iron stores.
- Hemoglobin is a poor indicator of iron status. Ferritin levels in serum or plasma directly reflect iron stores and are increasingly available.
- Studies find high prevalence of restless legs syndrome in blood donors, but with weak or inconsistent associations with iron status. Pica was shown to be more strongly correlated with donor iron status, but only in women. Fatigue and other reported correlates of low iron are understudied in blood donor populations.
- Significant heterogeneity exists for donor return behavior, donor productivity, and donor ability to recover the hemoglobin and iron lost through blood donation. Flexible, targeted strategies might achieve equivalent success to universal measures with potentially lesser impact on blood collections.