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Low hemoglobin deferral in blood donors

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Abstract

Low hemoglobin deferral occurs in about 10% of attempted whole blood donations and commonly is a consequence of iron deficiency anemia. Pre-menopausal women often have iron deficiency anemia caused by menstruation and pregnancy and have low hemoglobin deferral on their first donation attempt. Frequent donors also develop iron deficiency and iron deficiency anemia because blood donation removes a large amount of iron from the donor and the 56-day minimum inter-donation interval for donors in the United States is not sufficient for recovery of hemoglobin and iron stores. Other causes for low hemoglobin deferral range from a medically insignificant deferral of a woman with hemoglobin between 12.0 and 12.4 g/dL, which is within the normal reference range but below the 12.5 g/dL needed to donate blood, to anemia caused by an unrecognized malignancy in a “healthy” individual attempting to donate blood. The diverse causes of anemia in blood donors make it difficult to provide accurate information to donors about the cause of their low hemoglobin deferral and complicate implementation of programs to prevent them by blood collecting agencies. This article reviews how hemoglobin is measured and the demographics and causes of low hemoglobin deferral in blood donors. It provides recommendations for how blood collection agencies can provide donors with accurate information about the cause of their deferral and discusses programs that can be implemented to decrease these deferrals in regular donors.

Keywords

anemia; blood donor; deferral; hemoglobin; iron; ferritin; hepcidin

Introduction

The hemoglobin content of capillary blood obtained by fingerstick is used to pre-qualify blood donors in order to prevent donation by individuals with anemia. In the United States all donors, regardless of gender, age, race or ethnicity, are deferred from donating blood when their capillary hemoglobin is less than 12.5 g/dL, even though this allows male donors with anemia to donate (those with hemoglobin below 13.7 g/dL) while some non-anemic females are deferred (those with hemoglobin between 12.2 and 12.5 g/dL) [1]. Low hemoglobin deferral occurs in about 10% of all donation attempts making it the most

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Conflict of interest statement
AEM has provided educational talks about anemia for Siemens and Sysmex.

common cause of blood donor deferral [2]. However, interpretation of the medical importance of low hemoglobin deferral for an individual donor is complicated by several factors. These include:

1. Differences in the hemoglobin reference ranges for males and females, for various racial/ethnic groups and for older and younger individuals [1].
2. Differences in hemoglobin values obtained using capillary versus venous blood [3–5].
3. The poor correlation between capillary hemoglobin and body iron stores [6].
4. The high prevalence of iron deficiency in women of childbearing age and in frequent donors [7–9]

Thus, a low hemoglobin deferral may represent a medically insignificant finding, iron deficiency anemia from frequent blood donation, or the initial sign of a previously unrecognized and life-threatening disease [10].

Measurement of Capillary Hemoglobin

Historically, donor hemoglobin was assessed using the copper sulfate specific gravity method. Over recent years, quantitative methods that measure hematocrit or hemoglobin have been increasingly used with many blood collection agencies now using quantitative hemoglobin measurement. Hemoglobin is measured using point-of-care instruments that lyse the red cells, convert the hemoglobin to azidemethemoglobin and quantify the amount present using spectrophotometry [11]. These instruments can analyze capillary or venous blood thereby allowing comparison of samples obtained by different routes from the same donors at the same time. Two independent studies found that capillary hemoglobin underestimates venous hemoglobin when the value is slightly below the cut-off for blood donation of 12.5 g/dL. The authors of these studies suggested that lowering the hemoglobin cut-off values or performance of venous hemoglobin in donors with capillary hemoglobin below the cut-off value would allow collection of additional units of blood [3;4]. However, results from a third study indicate that fingerstick hemoglobin overestimates venous hemoglobin in donors with iron deficiency and venous hemoglobin <12.5 g/dL [5]; a condition particularly prevalent in female donors. Thus, lowering the current 12.5 g/dL cutoff may not be appropriate because it would increase collection of blood from iron deficient females. The data from these studies demonstrate that there is no perfect cut-off fingerstick hemoglobin value that will consistently disqualify donors with anemia and iron deficiency without also deferring non-anemic, iron replete donors. This reality further complicates the medical significance of a low hemoglobin deferral and the education that blood collecting agencies should provide these donors.

Demographics of Low Hemoglobin Deferral

Donors deferred for low hemoglobin are much less likely to return for future donations than donors that are not deferred. A study by Hillgrove and colleagues found that only 21% first-time donors with low hemoglobin returned to donate within three years, while 70% of those not deferred returned. Similarly, only 64% of repeat donors returned within three years following low hemoglobin deferral, while 91% of those not deferred returned [12]. Since low hemoglobin deferral is so common, it results in the apparently permanent loss of a large number of willing donors. Several studies have been performed to identify and quantify donor characteristics associated with low hemoglobin deferral in order to better understand how it can be prevented. A logistic regression model developed using data collected from 715,000 donors found that major demographic factors independently associated with low hemoglobin deferral include female gender, associated with 11-fold greater odds than males,

African American race, associated with 2.0 to 2.5-fold greater odds than Caucasians, and increasing age in men, associated with 1.5-fold greater odds per decade [2]. Increasing age has a much more muted effect in women because of menstruation and pregnancy induced iron deficiency in younger women. The odds for deferral decrease about 25% at menopause and then begin to increase with age in amounts similar to that observed in men. Several studies have found that differences in diet do not cause significant differences in the iron status of blood donors [8;9;13;14]. Blood donors smoking 10 or fewer cigarettes per day have been found to increase hemoglobin by 0.26 g/dL and smoking more than 10 per day produces an increase in 0.59 g/dL suggesting that the hemoglobin elevation associated with smoking may result in fewer low hemoglobin deferrals [15].

Interestingly, although a shortened inter-donation interval is associated with increased risk for deferral [16], increasing donation frequency is associated with decreased risk for deferral [14]. For example, women with six donations in the previous 12 months have only one-half the odds for deferral when compared to women with one donation in the same time period [2]. This finding has lead to the hypothesis that very high intensity donors are a self-selected population of individuals with genetic characteristics that allow for efficient absorption of dietary iron and hemoglobin synthesis. It was initially hypothesized that the H63D or the C282Y mutations in *HFE* associated with development of hemochromatosis may be responsible for this genetic variation; however several studies have now demonstrated that these mutations do not protect donors from low hemoglobin deferral [14;17;18]. These high intensity donors represent a unique population for further studies to identify previously unrecognized polymorphisms and biochemical pathways that regulate iron absorption and hemoglobin synthesis in humans.

Laboratory Testing to Identify Donors at Risk for Impending Low Hemoglobin Deferral

Laboratory testing of peripheral blood samples obtained at the time of donation has been used to identify donors with high risk for low hemoglobin deferral at their next donation. The goal of this testing is to identify those donors who would benefit from an intervention to prevent their impending deferral, such as decreasing the frequency of donation or providing iron supplements. Laboratory tests shown to be partially predictive include hemoglobin [19–21], hemoglobin trend over previous donations [19], red blood cell parameters [17;20;22–24], zinc protoporphyrin [25] soluble transferrin receptor [21], and ferritin [17;20–22;26]. Models that incorporate some laboratory test results, donor demographics and donation history to predict impending deferral have been developed [19;27;28]. While these models have shown some promise, effective models that can be widely implemented between different blood collection agencies in different countries remain to be developed [29].

Measurement of plasma hepcidin [30] represents a newer laboratory test that has been informative in understanding how blood donation alters iron physiology and may be useful in the management of frequent blood donors [26]. Hepcidin is the central iron regulatory hormone and regulates dietary iron absorption as well as the storage of iron within hepatocytes and macrophages that is used for new erythrocyte production [31;32]. Inappropriately low hepcidin produces increased dietary iron absorption and hereditary hemochromatosis [31], while inappropriately high hepcidin produces decreased dietary iron absorption and iron resistant iron deficiency anemia [33]. High intensity blood donors have very low to undetectable plasma hepcidin suggesting that they are absorbing maximal amounts of dietary iron to replace that lost from repeated blood donation [14]. Although plasma ferritin and plasma hepcidin levels correlate with each other, hepcidin is a more dynamic indicator of iron status than is ferritin in repeat blood donors [26] and in transfusion recipients [34]. This is because hepcidin is a hormone that responds to many physiological

stimuli including iron stores, inflammation and most importantly, erythropoietic activity [35], while ferritin is a relatively static measure of iron stores. As a consequence, ferritin continuously decreases with repeated blood donation in all donors [7] while hepcidin may or may not recover during the inter-donation interval [26]. Importantly, when hepcidin and ferritin were compared in a two-stage multivariable repeated measures regression model that accounted for variables such as gender, age, time since the last donation and the number of donations in the previous two years, the donors with low or decreasing plasma hepcidin had 0.51 g/dL lower hemoglobin than all other donors, including those with low ferritin and high hepcidin [26]. These data suggest that recovery of plasma hepcidin during the interdonation interval may serve as a marker indicating that an individual donor has absorbed sufficient dietary iron to restore their hemoglobin, even though they may have totally depleted iron stores. Similarly, continued low or decreasing hepcidin between donations may serve as a marker that the donor is not absorbing sufficient iron and is likely to have low hemoglobin in the future. Measurement of plasma hepcidin has become available for research purposes only in recent years and much remains to be learned about its relative diagnostic utility compared to other peripheral blood tests of iron status, particularly ferritin, in blood donors. Additional studies of larger and more diverse cohorts of blood donors are needed to further assess the utility of plasma hepcidin measurement in donor management.

Low Hemoglobin Deferral in Infrequent Donors

Each day about 40,000 people attempt to donate blood and undergo hemoglobin testing in the United States. Of these, approximately 30% are first time donors and many more are infrequent donors, who have not donated in the previous two years [15]. First time blood donor corrected fingerstick hemoglobin values compare very well with venous hemoglobin values from the National Health and Nutrition Examination Survey (NHANES), a large population based survey performed in the United States [15]. Thus, hemoglobin data obtained from blood donors represents a valuable public health resource for ongoing anemia surveillance. Anemia identified in a first time or infrequent donor should not be ignored. The vast majority of low hemoglobin deferrals are in women with iron deficiency caused by menstruation and pregnancy. However, important and unrecognized medical illnesses may also underlie the anemia in these donors. Non-malignant diseases that have been specifically identified in donors with low hemoglobin include, occult gastrointestinal bleeding, vitamin B12 deficiency, hyperthyroidism with thyrotoxicosis, diabetes mellitus, and Raynaud's syndrome [6]. Although anemia is not a sensitive indicator of malignant disease in blood donors with low hemoglobin deferral [36], previously unrecognized malignancies have been identified with published cases of essential thrombocythemia, acute lymphocytic leukemia and metastatic lung cancer identified in otherwise "healthy" individuals presenting to donate blood [6;10]. The many different causes for anemia identified in blood donors make it difficult to provide accurate, yet concise, information to the deferred donor. For males it is relatively simple because they do not have a biological blood loss that could result in iron deficiency anemia and hemoglobin below 12.5 g/dL represents significant anemia. All males with hemoglobin deferral should be referred to their personal physician for further evaluation of its cause, which may be frequent blood donation, and treatment. Recommendations for females are more complicated because of the high prevalence of iron deficiency anemia from menstruation and pregnancy and because some are deferred with a normal hemoglobin between 12.0 and 12.4 g/dL. An educational pamphlet designed using focus groups of deferred donors is available on-line [37], and the American Red Cross has recently updated their web site (http://www.redcrossblood.org/iron/deferred-donors) with accurate information and recommendations for donors with low hemoglobin.

Low Hemoglobin Deferral in Frequent Donors

Iron deficiency from repeated donation is the primary cause of low hemoglobin deferral in frequent donors. The only peripheral blood test performed to qualify donors is the fingerstick hemoglobin, which prevents donation by individuals with anemia but is a very poor predictor of iron deficiency [8]. Consequently, frequent blood donors, males and females, become iron deficient [7;8;16]. Donors are often advised to increase consumption of iron rich foods [10]. However, blood donation removes 200 to 250 mg of iron requiring the donor to absorb four to five mg of iron each day to replace that lost within the 56 day interdonation interval [13]. This amount of dietary iron absorption is about four-fold higher than baseline and cannot be consistently maintained solely by an iron rich diet [9;13;14]. Actual prevention of iron deficiency in regular donors will require oral iron supplementation or prolongation of the inter-donation interval [9]. Due to the high prevalence of iron deficiency in blood donors and the associated adverse effects, the AABB issued Association Bulletin #12-03 in September, 2012 recommending that blood collection agencies provide donors with information about the risks of post-donation iron deficiency and take action(s) to monitor, limit or prevent iron deficiency in donors.

Adverse Consequences of Iron Deficiency in Blood Donors

The side effects of iron deficiency in blood donors are significant. Pica is the compulsive consumption of non-food substances; most commonly ice but also other substances such as chalk, dirt, clay or cleanser. Individuals with severe pica have a continuous need to chew though out all waking hours. Those chewing ice may chew several pounds each day. About 10–15% of blood donors with iron deficiency have pica [38;39], which is much higher than is observed in the general population. Pica symptoms readily resolve within 5 to 8 days following initiation of oral iron therapy. It is important to note that the symptoms resolve regardless of the donor's iron status as assessed by ferritin measurement suggesting that pica is a more sensitive measure of functional iron deficiency than is this laboratory test [38]. Restless leg syndrome is a neurological disorder associated with iron deficiency that is characterized by an intense urge to move the legs, worsens with rest and interferes with sleep. Its symptoms are present in about 20% of donors but are not as uniquely associated with iron deficiency as are pica symptoms [38–40]. As comprehensively reviewed by Newman [41], iron deficiency is also associated with fatigue [42;43], decreased exercise capacity [44], adverse events related to pregnancy [45] and decreased performance over a broad range of cognitive tasks [46;47]. In addition, cortical development continues throughout the teenage years, and iron is critical for myelination during this process, even in apparently healthy adolescents [48;49]. Given these important consequences of iron deficiency, a particular concern of blood collection agencies should be the iron status of 16 and 17 year old blood donors, who account for more than 20 percent of the blood supply in many areas of the United States.

Prevention of Iron Deficiency in Blood Donors

Studies dating back to the 1970s have demonstrated that oral iron supplementation is safe and effective for prevention of blood donation induced iron deficiency [50;51]. Based on results from multiple carefully conducted research protocols, it appears that taking oral iron tablets daily for 60 days is adequate to replace the iron lost from donation [6;52–54]. Several issues need to be addressed in order for iron supplementation programs to be successfully and broadly implemented in community blood centers. The amount of oral iron recommended should be the minimal amount necessary to replace that lost from donation to minimize gastrointestinal side effects and improve compliance. Radtke and co-workers have shown that doses containing 20 mg elemental iron, which is approximately the amount in

common multiple vitamin tablets, are effective in preventing iron deficiency in men donating whole blood six times per year and in women donating four times per year [52]. Frequent donors are likely to benefit from iron supplementation. However, the definition of a “frequent” donor needs to be better defined. Many women will become iron depleted from a single donation [55], while many men can donate multiple times without becoming iron depleted [7]. One strategy to address this issue is to measure iron stores using ferritin testing in females donating two times per year and men donating three times per year and recommend or provide iron tablets to those with ferritin below a set cut-off value between 26 and 30 mg/L, that correlates well with low iron stores in otherwise healthy individuals [9;54;56]. Another advantage of strategies that use of ferritin to screen donor iron stores before recommending iron supplementation is that donors with unrecognized hemochromatosis will not be advised to take iron [55]. Donors deferred for low hemoglobin are also likely to benefit from iron supplementation [6;54]. While iron supplementation has been shown to be safe and effective, it may require careful medical assessment of some donors, particularly first-time and infrequent donors, so that the underlying cause of the anemia is identified and properly treated [10].

Prolonging the interdonation interval to allow for recovery of iron lost from blood donation will also prevent blood donation induced iron deficiency. It remains unclear how much it should be prolonged. It has been shown that there are no differences in iron stores and hemoglobin in first time donors and in reactivated donors, who have not donated in the previous two years [9]. However, for many donors, complete recovery of iron stores and hemoglobin lost from whole blood donation is six months or longer [17]. Recovery time is dependent on pre-donation ferritin and reticulocyte hemoglobin content [17;24;57]. There have been several studies evaluating laboratory tests of red blood cell indices and iron status to assess their value to identify and manage donors at high risk for developing blood donation induced iron deficiency [21;23;24;26;57;58]. The use of red blood cell parameters, such as reticulocyte hemoglobin content and percentage of hypochromic red blood cells, has been found to be useful in some studies [22;23], but not all [24], perhaps because some donors are able to adequately absorb dietary iron to restore hemoglobin even though they have severe deficiency of storage iron. The best single test for monitoring iron status in blood donors is probably ferritin, which is a highly specific and sensitive marker of depleted iron stores, especially in otherwise healthy individuals. In this regard, O’Meara and co-workers have reported that implementation of ferritin testing along with education of donors about iron supplementation, donation interval extension and/or dietary changes, significantly reduced iron deficiency and low hemoglobin deferrals in blood donors [58].

Conclusions

Low hemoglobin is the most common cause for deferral of whole blood donors. Each deferral causes the loss of at least one donation from a willing donor. The impact of the deferral is multiplied because, once deferred, many donors do not return to attempt another donation. When considering the underlying cause of the donor’s low hemoglobin, it is helpful to determine if they are a frequent or infrequent donor. Frequent donors often have iron deficiency anemia, which can be prevented by oral iron supplementation or prolonging the interdonation interval. Monitoring of iron stores in frequent donors by measurement of plasma or serum ferritin may be useful. Infrequent donors may have medical condition that produces anemia. Most commonly this is iron deficiency from menstrual and pregnancy associated blood loss in women of child bearing age. Anemia identified in men and post-menopausal women may signal an underlying medical illness requiring diagnosis and treatment. Continued work to understand the causes of anemia found in blood donors is needed to enhance the educational materials provided to donors deferred for low hemoglobin. Continued development and testing of interventions to prevent iron deficiency

are needed to identify programs that can be readily implemented in community blood centers. The end result will be fewer low hemoglobin deferrals and a healthier donor population.

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