

Severity of iron overload in hemochromatosis: effect of volunteer blood donation before diagnosis

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BACKGROUND: An effort was made to determine if volunteer blood donation before diagnosis decreases the severity of iron overload at diagnosis in persons with hemochromatosis.

STUDY DESIGN AND METHODS: A study was performed in 1089 persons in the United States with hemochromatosis who responded to a convenience sample survey and in 124 C282Y/C282Y hemochromatosis probands diagnosed during routine medical care.

RESULTS: Less than half of questionnaire respondents (46.2%) and probands (35.5%) reported that they had been volunteer blood donors; 5.4 percent and 4.0 percent, respectively, had donated >20 units of blood. In either subject group, there were no significant differences according to age in the mean numbers of units that needed to be removed by therapeutic phlebotomy to induce iron depletion in subgroups of men and women, respectively. Similarly, there was no significant correlation of units of voluntary blood donation or of therapeutic phlebotomy index (= therapeutic phlebotomy units ÷ age in years) with the number of therapeutic phlebotomy units needed to induce iron depletion. When questionnaire respondents were stratified by sex, there was no significant correlation of units of blood donation with the number of therapeutic phlebotomy units needed to induce iron depletion or with the therapeutic phlebotomy index.

CONCLUSION: Routine blood donation does not, on average, decrease the severity of iron overload in persons with hemochromatosis. These findings have implications for the understanding of the severity of iron overload and its complications in hemochromatosis, for advising persons with hemochromatosis about treatment, and for considering persons with hemochromatosis as possible blood donors.

Hemochromatosis occurs in approximately 1 in 200 white persons of Western European descent, and it increases the propensity to absorb excess iron. Iron overload associated with hemochromatosis can cause hepatic cirrhosis, primary liver cancer, arthropathy, diabetes mellitus, other endocrinopathic disorders, and a reduction in lifespan.^{1,2} These complications of iron overload can be avoided by early diagnosis and appropriate management.^{1,2} Because blood loss is the most effective way to reduce body iron stores, the preferred treatment for iron overload associated with hemochromatosis is therapeutic phlebotomy.^{1,2} Accordingly, it is also believed that persons with hemochromatosis who were volunteer blood donors before diagnosis may have less severe iron overload than those who were not donors, and therefore the former may have a reduced risk of developing complications of iron overload. Further, the identification of apparently healthy persons with hemochromatosis among blood donors in the United States,³ Australia,⁴ and Western Europe^{5,6} would appear to support this belief. However, persons diagnosed with hemochromatosis in the course of routine medical care delivery often have symptoms and organ dysfunction associated with complications of iron overload,^{1,7} and yet many have been blood donors.^{8,9} Taken together, these observations indicate that there is a need to define the relationship between vol-

ABBREVIATION: TPI = therapeutic phlebotomy index.

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Received for publication February 9, 2000; revision received June 6, 2000, and accepted June 7, 2000.

TRANSFUSION 2001;41:123-129.

untary blood donation before a diagnosis of hemochromatosis and the severity of iron overload at diagnosis.

We used two different study types and patient populations to determine if the results were consistent. We evaluated 1089 persons in the United States with hemochromatosis who responded to a convenience sample survey and 124 C282Y/C282Y hemochromatosis probands from central Alabama who were diagnosed during routine medical care delivery. We tabulated their age at diagnosis, the number of therapeutic phlebotomy units needed to induce iron depletion, and the therapeutic phlebotomy index (TPI), a measure of the severity of iron overload adjusted for age (= units of therapeutic phlebotomy ÷ age in years).¹⁰ We then analyzed the relationships of these data to the numbers of units of blood these persons donated as volunteers before their hemochromatosis was diagnosed.

MATERIALS AND METHODS

General criteria for selection of study subjects

The performance of this study was conducted according to the principles of the Declaration of Helsinki. The final questionnaire survey was approved by institutional review boards in participating institutions that distributed the questionnaire (Southern Iron Disorders Center, Brookwood Medical Center, Birmingham, AL; CDC, Atlanta, GA; and the Department of Medicine, LDS Hospital, Salt Lake City, UT).¹¹ The original survey from which the present data were extracted was conducted with four principal investigators in four separate institutions.¹¹ The respective institutions provided review for human-subjects protection based on a protocol that allowed for broad outreach to persons with hemochromatosis throughout the United States and other countries.¹¹ All subjects whose data are presented here were white, non-Hispanic persons living in the United States who were ≥18 years of age at the time of diagnosis of hemochromatosis. Nonwhite and Hispanic persons were excluded because 1) they represented <1 percent of persons who responded to the questionnaire; 2) measures of iron status differ among racial and ethnic groups^{12,13}; and 3) common primary iron overload disorders in nonwhite persons are phenotypically and genotypically different from hemochromatosis.^{14,15}

Hemochromatosis patients who responded to a questionnaire

We gathered this study population by conducting a convenience sample survey by mail of patients with hemochromatosis. To obtain a convenience sample, all original co-principal investigators¹¹ worked with patient advocacy and information organizations, blood and treatment centers, private physicians, and iron overload conferences; through the internet, other public media, and a toll-free telephone number; and with their respective patients to identify all

persons with hemochromatosis and to mail questionnaires to them. Questionnaires about diagnosis and treatment were mailed after a development process that included two focus groups and a field test. This sample included all persons with hemochromatosis whom we were able to locate within 1 year.¹¹ Although this study produced the largest known sampling of persons with hemochromatosis to date,¹¹ this sample is not necessarily representative of the entire population of persons with hemochromatosis.

Identifying information collected by questionnaire included first name, last name, complete address of residence (including country), date of birth, sex, race or ethnicity, level of education, and annual income. Persons who responded to our questionnaire were also asked to report their age at diagnosis of hemochromatosis, their complications of iron overload, their total volunteer blood donation (number of units) before diagnosis, and the number of units of blood that had been removed to achieve iron depletion and to maintain their iron stores at a low level after diagnosis.^{9,11} From September 1996 to September 1997, surveys were mailed to 3562 persons, of whom 2851 (80%) returned a questionnaire.^{9,11} We excluded the 16 percent of respondents who were not from the United States and 38 additional patients who did not state where they lived.¹¹ We also excluded persons who had porphyria cutanea tarda or forms of anemia sometimes associated with iron overload (e.g., thalassemia, sideroblastic anemia, hereditary spherocytosis) or who had received blood transfusion(s) that could have contributed to iron overload. From the remaining respondents, we selected data from all persons who indicated that they were adult, white, non-Hispanic Americans with hemochromatosis and who responded to all questions pertinent to the present study (n = 1089). However, we did not exclude persons because they had complications associated with iron overload (including hepatic cirrhosis, diabetes mellitus, arthropathy, or hypogonadotropic hypogonadism). We did not otherwise contact any questionnaire respondents, review their medical records, or evaluate them using physical or laboratory examinations.

Hemochromatosis probands diagnosed in routine medical care

We identified hemochromatosis probands from central Alabama who were diagnosed during routine medical care delivery during the interval from 1994 through 1998, who had completed iron depletion with therapeutic phlebotomy, and who were not included in our convenience sample questionnaire survey. We used the working diagnostic criterion for hemochromatosis of the American College of Pathologists: elevated fasting transferrin saturation (≥60% males, ≥50% females) on at least two occasions in the absence of other known causes^{1,7} (Table 1). We performed *HFE* mutation analysis in each proband after diagnosis¹⁶ and selected consecutive patients homozygous for the C282Y

TABLE 1. Characteristics of adult United States whites with hemochromatosis

Characteristics of sample groups	Questionnaire respondents	Alabama probands
Sample size	1089	124
Men; women	734; 355	72; 52
Age at diagnosis (years)(mean \pm SD)	48 \pm 13	49 \pm 13
Diagnosis of hemochromatosis	Self-report (referred from physicians, patient advocacy groups, and blood procurement centers)	Repeated transferrin saturation without other cause ($\geq 60\%$ men, $\geq 50\%$ women) and homozygosity for C282Y <i>HFE</i> mutation
Diagnosis of complications of iron overload	Self-report based on physician diagnosis of arthropathy, diabetes mellitus, or hepatic cirrhosis	Arthropathy: characteristic degenerative, hypertrophic changes in 2nd or 3rd metacarpophalangeal or proximal interphalangeal joints, hips, or knees (with or without chondrocalcinosis) without other etiology; Hepatic cirrhosis: bridging fibrosis observed on biopsy specimens stained with Masson's trichrome technique; Diabetes mellitus: fasting blood glucose repeatedly ≥ 140 mg/dL (or ≥ 12); Other endocrine disorder: limited to hypogonadotropic hypogonadism
Presence of complications attributed to iron overload		
Arthropathy (n)	26.5% (289)	18.5% (23)
Hepatic cirrhosis (n)	8.3% (90)	12.1% (15)
Diabetes mellitus (n)	5.3% (58)	4.8% (6)
Other endocrine disorder (n)	7.1% (77)*	8.0% (10)

* Self-reported physician diagnosis of any of the following: hypogonadotropic hypogonadism, impotence, loss of libido, or premature menopause. This category does not include thyroid, parathyroid, adrenal gland, or other endocrine organ disease.

mutation of *HFE*. Iron overload was defined as evidence of systemic iron overload shown by an otherwise unexplained, elevated serum ferritin concentration (≥ 300 ng/mL in men, ≥ 200 ng/mL in women), increased hepatic iron content determined by using hepatic biopsy specimens, or ≥ 4 g of iron mobilized by phlebotomy.^{7,13} For each proband, we tabulated the units of blood removed by therapeutic phlebotomy (1 unit of blood = 450-500 mL, equivalent to approx. 200 mg of iron). Complications associated with iron overload were assessed as previously described^{7,17}; criteria used to establish these diagnoses are displayed in Table 1.

Voluntary blood donation before diagnosis of hemochromatosis

We tabulated the numbers of units of whole blood that each of our questionnaire respondents and Alabama probands reported that they had donated as volunteers before they were diagnosed with hemochromatosis.

Statistical considerations

Data were analyzed with software (Epi Info version 6.0.25,¹⁸ CDC, Atlanta, GA; and Excel, Microsoft, Redmond, WA). Descriptive results are displayed (in Table 1) as mean \pm 1SD (range) or as percentages (n). Mean values for ages and numbers of units of therapeutic phlebotomy were rounded to the nearest integer for presentation. Data from men and women were analyzed separately because the severity of iron overload in men with hemochromatosis is significantly greater on average than that in women.^{10,16,19,20} We divided our data from questionnaire respondents by the sex of the respondent, and into additional subgroups based on age at diagnosis of hemochromatosis. Data from Alabama probands were divided by the respondent's sex only; the proband data were insufficient for dividing into subgroups based on age. The TPI (= therapeutic phlebotomy units \div age in years)¹⁰ was calculated for all persons in this study. Comparisons were made using ANOVA or coefficient of correlation (*r*), as appropriate. Values outside a 95% CI were defined as significant.

RESULTS

General characteristics of study subjects

A preliminary analysis of the questionnaire data indicated that respondents included in the present study resided in all 50 states of the United States. The responses were not evenly distributed, but

tended to be centered in geographic areas corresponding to those of the co-principal investigators who participated in design of the original questionnaire project.¹¹ In the present report, ≥ 3.0 percent of all responses came from persons who reported that they resided in Alabama, California, Colorado, Florida, Georgia, Illinois, New Jersey, New York, Pennsylvania, Texas, and Utah. On average, these persons had been diagnosed with hemochromatosis 7 years before they responded to our questionnaire. There were no significant differences in signs, symptoms, age at diagnosis, methods of diagnosis, or units of blood removed to induce iron depletion among respondents by major geographic areas of the United States (Northeast, South, Midwest, and West). We estimate that less than 2 percent of the questionnaire respondents were diagnosed in a screening program, based on the geographic distribution of our questionnaires and completed or ongoing screening programs for hemochromatosis.

The average age at diagnosis of hemochromatosis was similar in questionnaire respondents and Alabama probands, although there was a greater percentage of men among the questionnaire respondents (67.4% vs. 58.1% Alabama probands) (Table 1). Different criteria were used to establish the diagnoses of complications of iron overload in the two study groups. However, the percentages of persons with arthropathy, hepatic cirrhosis, diabetes mellitus, and other endocrinopathic disorders appeared to be similar in the two groups. Forty-one questionnaire respondents (3.8%) and none of our Alabama probands indicated that they had taken iron supplements for a total of 6 or more months at some time during their lives.

Voluntary blood donation before diagnosis of hemochromatosis

Among the questionnaire respondents, 53.4 percent of men (n = 392) and 31.3 percent of women (n = 111) had been blood donors before their diagnosis. Among Alabama probands, 47.2 percent of men (n = 34) and 19.2 percent of women (n = 10) had been blood donors. Among questionnaire respondents, men aged 40 to 60 donated the greatest numbers of blood units. Among questionnaire respondents, 48 men (6.4%) and 11 women (3.1%) donated >20 units of blood before diagnosis. Among Alabama probands, 4 men (5.6%) and 1 woman (1.9%) donated >20 units of blood before diagnosis (Table 2).

Relationship of voluntary blood donation before diagnosis of hemochromatosis to iron overload

Questionnaire respondents. Among age-based subgroups, there were no significant differences in the mean numbers of units removed by therapeutic phlebotomy to induce iron depletion in men and women (ANOVA) (Table 3). Among all subjects, there was no significant correlation of units of

blood donation before diagnosis or TPI and the number of therapeutic phlebotomy units needed to induce iron depletion ($r = 0.02$), nor was there a difference when we stratified our subjects by sex ($r = -0.04$, men; $r = -0.02$, women). We also performed a linear regression analysis and ANOVA in the 58 questionnaire respondents (48 men, 11 women) who had donated >20 units as volunteers. In this subset, there was no significant relationship of units removed by therapeutic phlebotomy to induce iron depletion (and of TPI) to units donated before diagnosis ($r = 0.23$, therapeutic phlebotomy units; and $r = 0.23$, TPI).

Alabama probands. When these subjects were grouped according to the units of blood donated before diagnosis, we did not observe significant differences in the mean numbers of units removed by therapeutic phlebotomy to induce iron depletion in men or women (Table 3). There was no significant correlation of units of blood donation before diagnosis and the number of units removed by therapeutic phlebotomy to induce iron depletion ($r = -0.13$, men; $r = -0.16$, women) (Fig. 1). Similarly, we found no significant relationship of TPI with the number of units removed by therapeutic phlebotomy to induce iron depletion in men or women using ANOVA and correlation coefficient analyses (data not shown). We also used computerized methods to approximate these data with exponential, logarithmic, and polynomial curves, but a significant fit could not be obtained (data not shown). There were insufficient numbers of Alabama probands who had donated >20 units to permit a meaningful analysis of this subset.

DISCUSSION

Our data show that voluntary blood donation before diagnosis of hemochromatosis is not significantly correlated with the number of therapeutic phlebotomy units needed to induce iron depletion. Untreated persons with hemochromatosis typically absorb increased fractions of inorganic and heme iron from food and drink. This often leads to the development of iron overload, because excretory mechanisms for iron are very limited.³ After phlebotomy of persons with hemochromatosis, however, there is a further, marked increase in the absorption of inorganic and heme iron.²¹⁻²⁴ This could explain why most persons in our study who donated blood before diagnosis apparently absorbed sufficient quantities of iron to re-establish their predonation iron stores, even when their donation rate was relatively high. Our results imply that the “volunteer” blood donation sometimes recommended by physicians and patient advocacy groups

TABLE 2. Units of volunteer blood donation before diagnosis of hemochromatosis in persons stratified by age and sex*

Questionnaire respondents	Donated units				Totals
	0	1-10	11-20	>20	
Men					
<40 years old	54.9 (107)	33.8 (66)	8.7 (17)	2.6 (5)	100.0 (195)
40-60 years old	41.8 (185)	33.7 (149)	16.1 (71)	8.4 (37)	100.0 (442)
>60 years old	51.5 (50)	25.8 (25)	16.5 (16)	6.2 (6)	100.0 (97)
Women					
<40 years old	70.1 (54)	26.0 (20)	2.6 (2)	1.3 (1)	100.0 (77)
40-60 years old	66.5 (127)	26.2 (50)	4.2 (8)	3.1 (6)	100.0 (191)
>60 years old	72.5 (63)	17.2 (15)	5.7 (5)	4.6 (4)	24.5 (87)
Alabama probands					
Men, 49 ± 13 years old	52.8 (38)	22.2 (16)	19.4 (14)	5.5 (4)	100.0 (72)
Women, 49 ± 13 years old	80.8 (42)	15.4 (8)	1.9 (1)	1.9 (1)	100.0 (52)

* Values given as percentage (n). These data represent volunteer whole-blood donation by persons subsequently diagnosed with hemochromatosis, stratified by age and sex, as indicated. Percentages indicate the proportion of persons in each age cohort. The numbers of Alabama probands were insufficient to make meaningful subgroup comparisons based on age at diagnosis. Therefore, the mean age at diagnosis (years ± 1SD) for male and female Alabama probands is displayed.

TABLE 3. Units of therapeutic phlebotomy to induce iron depletion in hemochromatosis: stratification by voluntary blood donation, age,* and sex

Questionnaire respondents	Donated units			
	0	1-10	11-20	>20
Men				
<40 years old (n = 195)	32 ± 40	37 ± 26	31 ± 25	40 ± 39
40-60 years old (n = 442)	35 ± 38	41 ± 38	36 ± 34	36 ± 37
>60 years old (n = 97)	35 ± 32	41 ± 38	36 ± 38	24 ± 9
Women				
<40 years old (n = 77)	27 ± 29	28 ± 34	19 ± 25	20 ± 0
40-60 years old (n = 191)	30 ± 32	38 ± 35	21 ± 20	21 ± 15
>60 years old (n = 87)	28 ± 25	18 ± 14	26 ± 23	44 ± 12
Alabama probands				
Men, 49 ± 13 years old (n = 72)	36 ± 23	24 ± 15	27 ± 17	23 ± 19
Women, 49 ± 13 years old (n = 52)	20 ± 22	10 ± 8	17	0†

* The age ranges (questionnaire respondents) or mean ages ± 1 SD (Alabama probands) presented are those at the time of diagnosis (n). The numbers of Alabama probands were insufficient to make meaningful subgroup comparisons based on age at diagnosis. Tabular data represent units of blood required to induce iron depletion (mean ± 1SD).

† A woman who donated 30 units as a volunteer before diagnosis of hemochromatosis did not require iron depletion therapy.

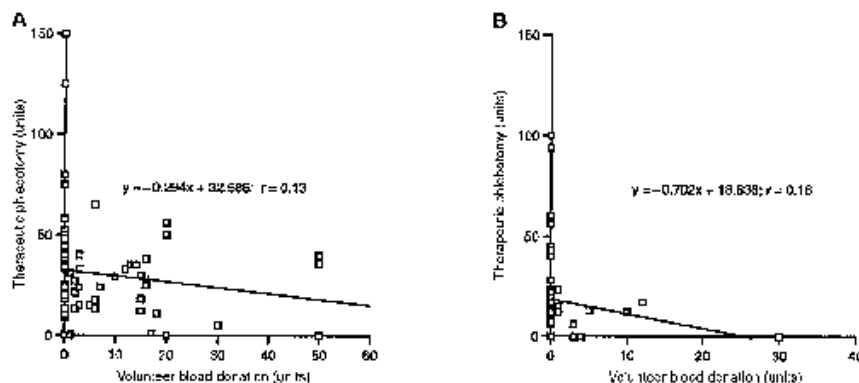


Fig. 1. Scatter plots of units of prediagnosis volunteer blood donation versus the number of units that needed to be removed by therapeutic phlebotomy to induce iron depletion at diagnosis of hemochromatosis in 72 men (A) and 52 women (B) who were C282Y homozygotes.

as treatment for American hemochromatosis patients^{11,25} is unlikely to prevent the development of iron overload, even when hemochromatosis is diagnosed early. It also seems likely that other factors influence the severity of iron overload at diagnosis of hemochromatosis more than volunteer blood donation.^{1,10,16,19,20,26}

Our present study design does not permit a determination of whether complications of iron overload occur less frequently among persons with hemochromatosis who have been volunteer blood donors before diagnosis. It is possible that this is the case, because the risks of developing hepatic cirrhosis, diabetes mellitus, and hypogonadotropic hypogonadism in hemochromatosis are positively associated with the severity of iron overload.^{1,2} However, the development and progression of arthropathy are less clearly associated with the severity of iron overload and therapeutic phlebotomy.^{1,2} Further, co-morbid condi-

tions unrelated to iron overload that significantly influence the severity of these complications are also relatively common among persons with hemochromatosis,^{1,2,7,20,27} but are unlikely to be affected directly by blood donation or therapeutic phlebotomy.

Many apparently healthy persons diagnosed with hemochromatosis in screening programs of blood donors and other populations are young and do not have severe iron overload.^{1,3} Further, the progression of iron overload is slow in some untreated persons with hemochromatosis.²⁸⁻³⁰ It is possible that our study subjects donated blood less frequently than persons diagnosed with hemochromatosis in screening programs, or that we preferentially selected persons with hemochromatosis who express a more severe clinical phenotype. However, this seems unlikely, because our recruitment methods for questionnaire respondents and Alabama probands were very different, and yet the results obtained from these two groups were similar. Our results therefore imply that screening volunteer blood donors by phenotypic testing is unlikely to result in an underestimation of the frequency or penetrance of hemochromatosis, because their iron stores, on average, are not significantly affected by their blood donations. Nonetheless, the relatively small size of some of our subgroups could account for some of the nonsignificant differences observed in the present study.

The FDA limits the frequency of volunteer donation to an 8-week interval.³¹ This regulation is intended to prevent iron depletion of donors, although the body iron stores of many normal donors nonetheless decrease significantly with routine volunteer (allogeneic) or autologous blood donation.³²⁻³⁵ In contrast, our present data indicate that iron absorption in many persons with hemochromatosis is sufficient to replenish iron stores to predonation levels when phlebotomy is performed no more frequently than every 8 weeks. Persons with hemochromatosis can now undergo weekly therapeutic phlebotomy by prescription at blood-collection stations if they meet the criteria for volunteer donation and if their respective stations have obtained a "variance" from existing regulations³⁶ from the FDA.³⁷ It is also necessary to monitor the progress of their phlebotomy by measuring Hb or Hct and serum ferritin concentrations.² In a previous study, 69 (33%) of 211 hemochromatosis

probands were ineligible as potential blood donors because of at-risk behavior, receipt of blood transfusion within the last year, infectious diseases, insufficient yield or intolerance of phlebotomy, advanced chronic disease, or noncompliance.⁸ Of the remaining potentially eligible probands, 86 of 142 underwent iron-depletion therapy by weekly phlebotomy and were evaluable for each phlebotomy session and blood unit. Sixty-five percent of these units were potentially suitable for transfusion.⁸ Thus, the total units of blood potentially available for transfusion would have been 44 percent of those removed by therapeutic phlebotomy (67% donor eligibility \times 65% unit suitability) during iron-depletion therapy.⁸ This was significantly lower than the 88 percent estimated for volunteer donors from an adjacent geographic area.⁸ Most persons with hemochromatosis require the phlebotomy of only 1 to 4 units yearly to maintain iron stores at low normal levels after induction of iron depletion.^{1,2,8-10,16} Thus, the percentage of units collected from them during maintenance therapy that are potentially suitable for transfusion (59% = 67% donor eligibility \times 88% unit suitability) approaches that in normal volunteers.⁸

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