DETECTION AND PREVENTION OF IRON DEFICIENCY IN DONORS OF BLOOD (BLOOD COMPONENTS)

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The problem of iron deficiency among donors is relevant and directly affects the provision of hemocomponents to the blood service. Donors, being a risk group for the development of iron deficiency, are examined before donation, including a study of hemoglobin levels. However, there is no information about the state of iron stores, when depleted, iron deficiency anemia develops. In turn, anemia is a contraindication to donation and, therefore, leads to medical exemptions from donation. The purpose of the study was to evaluate the main indicators of iron metabolism in donors of blood and (or) blood components at risk of developing latent iron deficiency. The examination of 174 donors included a hemogram, assessment of the level of hemoglobin, serum ferritin (SF), transferrin, and soluble transferrin receptors. When assessing the intensity of changes in reserve and transport iron indicators, 228 deviations from the reference range were analyzed. The criterion for the risk of developing iron deficiency was hemoglobin values at the lower limit of normal (130–135 g/l in men and 120–125 g/l in women) and the threshold level of ferritin (30 μg/l in male donors and 20 μg/l in women). The risk group included 58.3% of young donors — women who donate blood 1–2 times during the year ($p < 0.01$) and 66.6% ($p < 0.01$) of donors — men who donate blood regularly throughout 4 and > years. The average ferritin level in male donors was 27.37 μg/l ($p < 0.02$) and lower than the reference values. It is concluded that it is advisable to assess the indicators of iron metabolism in donors in the case of borderline hemoglobin levels, in women of reproductive age after 2 blood donations and in men with the number of donations ≥ 10. To replenish the iron depot in the body, when iron deficiency is detected in donors, it is necessary to consider the issue of prevention.

Keywords: iron deficiency, donation, risk, ferritin, transport iron

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ВЫЯВЛЕНИЕ И ПРОФИЛАКТИКА ЖЕЛЕЗОДЕФИЦИТНОГО СОСТОЯНИЯ У ДОНОРОВ КРОВИ (КОМПОНЕНТОВ КРОВИ)

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Проблема дефицита железа среди доноров является актуальной и напрямую влияет на обеспечение гемокомпонентами службы крови. Доноры, являясь группой риска по развитию железодефицитного состояния, проходят обследование перед донацией, включающее исследование уровня гемоглобина. При этом отсутствует информация о состоянии запасов железа, при истощении которых развивается железодефицитная анемия. В свою очередь анемия является противопоказанием к донорству и, следовательно, приводит к медицинским отводам от донации. Целью исследования было оценить основные показатели обмена железа у доноров крови и (или) компонентов крови, подверженных риску развития латентного железодефицита. Обследование 174 доноров включало гемограмму, оценку уровня гемоглобина, сывороточного ферритина (СФ), трансферрина, растворимых рецепторов трансферрина. При оценке интенсивности изменений показателей запасного и транспортного железа были проанализированы 228 отклонений от референтного диапазона. Критерием риска развития железодефицитного состояния были значения гемоглобина у нижней границы нормы (130–135 г/л у мужчин и 120–125 г/л у женщин) и пороговый уровень ферритина (30 мкг/л у доноров-мужчин и 20 мкг/л у женщин). В группу риска вошли 58,3% молодых доноров-женщин, сдающих кровь 1–2 раза в течение года ($p < 0,01$) и 66,6%, ($p < 0,01$) доноров-мужчин, сдающих кровь регулярно в течение четырех и более лет. Средний показатель ферритина у доноров-мужчин — 27,37 мкг/л ($p < 0,02$) был ниже референсных значений. Сделан вывод о целесообразности оценки показателей обмена железа у доноров в случае пограничного уровня гемоглобина, у женщин репродуктивного возраста после 2 донации крови и мужчин с числом донаций ≥ 10. Для восполнения депо железа в организме при выявлении железодефицита у доноров необходимо рассматривать вопрос о профилактике.

Ключевые слова: железодефицит, донация, риск, ферритин, транспортное железо

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In every blood donation, iron loss can promote latent iron deficiency (LID) in recurrent donors, especially among women. Progression of iron deficiency results in iron deficiency anemia, which subsequently becomes the reason for temporary exemption of donors from donation [1–6]. Iron deficiency can be accompanied with such symptoms as weakness, absent-minded behavior, somnolence, fatigue, taste disturbances, skin dryness, severe loss of hair, fragility and deformity of nail plates, gastrointestinal disturbances, menstrual disorder in females, etc. It is known that not only whole blood collection is accompanied with iron loss. Apheresis damages red blood cells, which go back to the blood stream [7]. Thus, when platelets are donated using apheresis, donors lose up to 100 ml of blood. Then there is risk that iron deficiency can be developed. The majority of values (Hb, HCT, transferrin, transferrin saturation and ferritin) were significantly lower than the reference values [8]. With the increased interval between donations, the percentage of donors with iron deficiency dropped [9]. An increased rate of apheresis can trigger low iron [10]. It should be noted that after donation iron deficiency anemia can be developed in 0.14–0.8% of male donors only. For female donors, the value is a sequence higher. It is 1.7–17.4%. Donation of 450 ± 10% ml of whole blood results in Hb drop in a donor by 3.5–14 g/L from baseline. Each donation results in the loss of 200 to 250 mg of iron. It is about 5-6% of entire iron stores in the body [11]. Maximum Hb drop is seen at day 5 post-donation. It gets gradually replenished to the pre-donation value at an average of about 30 days. To synthesize new Hb molecules, a healthy donor uses the available iron stores. Taking into account stages of iron deficiency, WHO recommends to determine the concentration of both Hb and ferritin [11,12] in order to diagnose iron deficiency among people who look healthy. It happens because plasma/serum ferritin is positively correlated with total iron stores in the lack of inflammation [13–15]. At the stage of latent iron deficiency, lab values of serum ferritin (SF) have more pronounced changes. Not only depletion of iron depot such as low serum ferritin but also low iron concentration in serum and carrier proteins are recorded. Decrease of serum ferritin below 15 μg /l in adults (adjusted below 30 μg/l) and 70 μg /l in adults with inflammatory diseases means inevitable drop of Hb in the future [12].

By now, numerous works demonstrating ferritin blood test results in donors have been published. Retrospective trials with outcomes obtained during 10 and more years are of the greatest interest. Among donors with high rate of donations, 9.4% of males and 25.7% of females had low ferritin levels. An increased donation interval (up to 6 months in males and 8 months in females) results in low risk of iron deficiency [15]. Meanwhile, authors assess iron deficiency depending on gender, age, postmenstrual period, quantity and rate of donations in donors of whole blood only. They, however, fail to assess the values in platelet donors. Thus, it seems relevant to assess the effect of donation type (including mixed donations), donation rate, age, gender and donor experience on the values of iron exchange due to a higher volume of highly specialized medical aid and, as a consequence, whole blood and platelet concentrate banking.

The purpose of the study is to assess the principal values of iron exchange in donors of blood and (or) blood components at risk for developing latent iron deficiency.

METHODS

174 donors of blood and blood components (101 males and 73 females) at the age of 19-62 years (median of 35 years) were investigated. Inclusion criteria: age ≥18 years, weight over 50 kg, readiness to sign an informed consent form (ICF) and refusal from participation in other clinical trials. To examine iron exchange in donors, six groups were formed depending on donor experience, rate and type of donations (blood, platelets, mixed donations for those who donate whole blood, plasma and platelets for four and over years on a constant basis). All patients were divided into groups according to gender and age. Donors were distributed into three groups: under 25 (students), 25 to 45 (regular donors, middle group) and above 45 years (active donors). A group consisting of 130 blood donors was isolated to determine an effect produced by a number of donations on a donor's body. Donors were recruited and examined as specified in regulatory documents. Exclusion criteria: temporary or constant contraindications to blood donation established on the day of assumed donation as per regulatory documents [16]. Hematological, biochemical and statistical methods of research were used in the work. A set of reagents (Coulter LH Series Retic PAK Reagent Kit; US) (Roche Diagnostics GmgH; Germany) was utilized to estimate iron exchange. Hemogram values were assessed using the Medonic M-Series (Boule Medical AB; Sweden) Hematology Analyzer, medical devices registered under the established order (S-Monovette vacutainer tubes 2.6 ml K2EDTA labeled as REF 04.1901.001 (Sarsted AG Co.KG Germany); microtubes 1.5 ml, Sarsted, Eppendorf type, 39*10.8 mm with RR graduation, neutral with Safety cap (Sarsted AG Co.KG; Germany). Serum ferritin was examined to assess iron stores in donors by immunoturbidimetric technique. Concentration of transport iron was analyzed based on serum iron (SI), serum transferrin (ST), total (TIBC) and unsaturated iron-binding capacity (UIBC) of serum and such an estimate as Transferrin Saturation Index (TSI). Cobas Integra 400 plus Biochemistry Analyzer (Roche Diagnostics; Switzerland) was used to perform studies. Soluble transferrin receptors (sTfR) were determined using automated immunochemistry analyzer (Beckman Coulter LH Series; Coult USA company) by immunoenzyme technique. Statistical analysis was done using SPSS 24.0 program (Dell; USA). The obtained results were represented as a median, first and third quartiles. Mann-Whitney test was used to assess significance of parameters between the groups. Intragroup differences were assessed using pair-wise comparison and Wilcoxon test. Differences were considered statistically significant when the probability of error was not exceeding 0.05 ($p < 0,05$).

RESULTS

It was found out that 174 donors distributed into six groups depending on the type, rate of donation, gender and age, blood picture values were almost similar to reference values. During assessment of intense changes in spare and transport iron values, 228 abnormal values from the reference range were analyzed (Table 1).

Comparative analysis of examination results of the principal values of iron metabolism in the investigated donors has shown that the level of ferritin is the most informative value. Levels of ferritin below the reference values were seen in donors of all groups, except for primary male donors (Figure).

Low ferritin levels below the reference values were seen in 39 of investigated males of 101 (38.6%). Depleted iron stores were detected in 32 of investigated females of 73 (43.8%). Level of ferritin, which identifies the absence of body iron stores (less than 12–15 μg/l), was seen in 14 male donors (13.9%) and 19 female donors (26%).

Borderline values of Hb were seen in 19.8% of regular donors of blood and blood components ($n = 174$). It was 119 g/l

Table 1. Factors of latent iron deficiency in different groups of donors of blood (blood components)

Risk factor of latent iron deficiency	HGB, low borderline	SF Normal value	SF ↓ Latent iron deficiency	SI ↓	ST ↑	TIBC ↑	TSI	sTfR ↑	Total deviations
Deviations from reference values	30 (17.2%)	103 59.2%	71 (40.8%)	25	10	41	36	15	228
TYPE of donation:									
Primary	4	26	3	2	–	–	2	–	11
Donations 1–2 times during a year	5	13	11 (45.8%)	4	1	7	7	3	38
Regular, every 3 years	4	10	5 (33.3%)	2	3	9	5	2	30
Regular, every 4 and more years	10	21	30 (58.8%)	9	3	14	12	8	86
Mixed donations	3	13	6 (31.6%)	4	1	4	5	–	23
TCP donors	4	20	16 (44.4%)	4	2	7	5	2	40
Gender of donors:									
Males	10 (26.3%)	62	39 (38.6%)	14	7	22	21	9	122
Females	20 (66.7%)	41	32 (43.8%)	11	3	19	15	6	106
Age of donors:									
Younger than 25 years	8	21	14 (40.0%)	6	1	8	10	2	49
25–45 years	18	61	46 (43.0%)	10	5	23	18	9	129
Over 45 years	4	21	11 (34.4%)	9	4	10	8	4	50

in three females (1.7%) from various groups only. Donors with Hb values at the lower limit of normal (130 g/l in males and 120 g/l in females) with deviations of 3–6 g/l and donors of thrombocytapheresis (TCP) often have a tendency to depletion of iron stores in case of continuous subsequent donations and are, consequently, at risk of latent iron deficiency [13]. Hb values at the lower limit of normal and low SF levels were detected in 30 (42.2%) of 71 donors. Borderline values of Hb and threshold values of ferritin (30 μg/l in male donors and 20 μg/l in females) were risk criteria for iron deficiency (Table 2).

The group at risk of iron deficiency included 58.3% of young female donors who gave their blood 1–2 times per year and 54.4% of female apheresis platelet donors (Table 3). The risk of early latent iron deficiency was detected among male (66.6%) and female (50%) donors who gave blood during four and over years on a regular basis. Mean value of ferritin in male donors was 27.37 μg/l, which is below the reference values (30.0 μg/l).

The values of iron exchange were analyzed in 130 blood donors to detect the effect of the number of donations on iron deficiency. Low SF was noted among three investigated female donors within the control group (primary donors, 28 people) during the first donation. Following the second donation, female donors (n = 11) had an increased level of sTfR (4.28 ± 0.26 g/l), TIBC and UIBC in a significant drop of ferritin (17.38 ± 3.2 μg/l). The reasons can include significant changes in the values of iron exchange during the first year of donation, which are particularly pronounced among female donors. It is known that females have less iron stores in the body (35–40 mg/kg) as compared to males (50 mg/kg body mass) [17]. The third blood donation was followed by a progressive drop of SF concentration among male donors with a subsequent increase of sTfR and TIBC. It is established that iron stores gradually decrease with increased donation intensities. This is particularly notable for the concentration of SF in males. According to the studies, a significant decrease of SF (28.1 ± 4.4 μg/l; n = 28) below reference values (30.0–400.0μg/l) was detected among male donors after ten blood donations. The changes are less evident in female donors. This is probably associated with an increased interval between donations. Low level of SF was found after the second blood donation

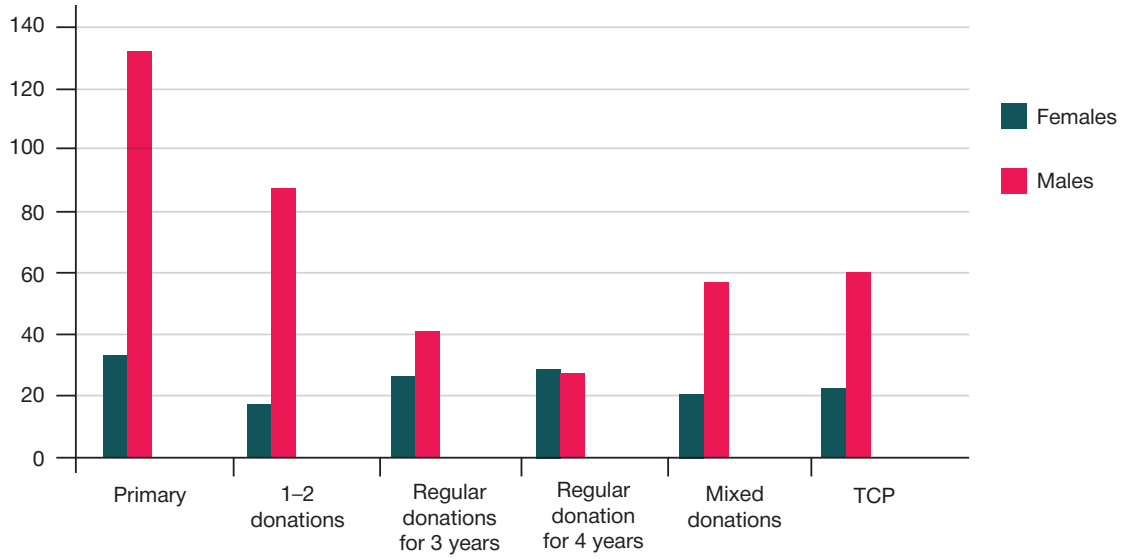

Fig. Changes in the level of serum ferritin (μg/l) among donors from the investigated groups

Table 2. Risk criteria of latent iron deficiency in different groups of blood (blood component) donors, (M ± SD)

Value	Primary (control)	1–2 times a year	Regular 3 years	Regular 4 years and >	Mixed donations	TCP
Females	*n* = 14	*n* = 12	*n* = 6	*n* = 24	*n* = 6	*n* = 11
Ferritin, μg/l	33.3 ± 4.5 (9.3–65.9)	**17.38 ± 3.2* (3.5–37.2) *p* = 0.0042***	26.8 ± 5.4 (14.5–47.8)	28.9 ± 3.5 (9.00–77.4)	**20.3 ± 5.1* (2.4–34.3) *p* = 0.007***	22.8 ± 5.13 (9.6–55.3)
HGB, g/l	131.2 ± 1.9 (120–144)	131.1± 2.8 (121–150)	133.0 ± 4.6 (117–146)	130.9 ± 1.8 (119–153)	132.2 ± 3.9 (121–145)	128.7 ± 2.3 (121–132)
Males	*n* =15	*n* =12	*n* = 9	*n* = 27	*n* =13	*n* = 25
Ferritin, μg/l	132.3 ± 24.5 (33.3–379.0)	88.2 ± 34.0 (8.5–296.0)	41.7 ± 9.9 (13.0–101.8)	**27.37 ± 3.02* (7.2–72.0) *p* = 0.0014***	57.8 ± 8.9 (14.8–122.0)	60.9 ± 8.77 (5.8–177.9)
HGB, g/l	154.3 ± 3.83 (128–168)	148.7 ± 2.8 (132–164)	142.9 ± 4.1 (130–167)	146.5 ± 1.9 (132–170)	150.6 ± 2.3 (134–163)	147.7 ± 1.53 (128–158)

Note: * $p < 0.01$ — statistical significance in the group of primary donors.

with a subsequent significant drop below the reference range. This is the basis for determination of SF during examination of donors after the second and every tenth blood donation. Thus, borderline allowable values of Hb and (or) HCT prior to blood or platelet donation (↓ in 30 people), number of donations (6–10) [13] and duration of donor experience (3–4 years) [13] produced an effect on iron metabolism in donors. Depleted iron stores were seen among young female donors between the second and sixth donations, and among male donors with 10 donations and more.

Thus, periodic control of SF level is required for timely diagnostics of aberration of iron metabolism, including in case of normal content of Hb in blood. The reason for iron deficiency in donors of blood and blood components is the loss of certain amount of iron during every donation and its slow restoration from the incoming food [18]. During donations, donors have to consider an issue about prevention of iron deficiency to replenish the iron depot in the body. Signs of LID will require preventive activities and, if necessary, an increased interval between donations. This will promote preservation of a donor capacity. Preventive activities that can decrease the risk of LID are shown in Table 4.

DISCUSSION

Iron deficiency is a serious threat to donor potential. In accordance with the obtained data, latent iron deficiency in donors is developed due to duration of donor experience and short intervals between donations. To preserve donor potential, donors are examined to detect depleted iron stores. Common ferritin and alternative values of iron exchange (transferrin, soluble transferrin receptors) can be used as markers. All donors with borderline Hb level, female donors of a reproductive age after the second donation and males with ≥ ten donations have to measure the levels of SF. The basic principles of LID treatment include correction of reasons, which form the basis of iron deficiency, and elimination of iron deficiency in blood and tissues [14, 15].

According to our data, the level of SF below the reference range requires correction of this value due to an increased interval between donations and intake of iron preparations. However, the treatment strategy can result in lower stores of donor blood components at blood transfusion centers (blood banks). Thus, an increased interval between donations resulted in lower stores of donor blood by 8% in the first year. In five years, the value was 4.7% [19]. A number of donors with iron deficiency and anemia dropped by 13.6% and 29.3% respectively. The treatment strategy produced a slight effect on blood stores (–3.2% in 5 years). In our opinion, this is a long-term approach. In 10 years, it will allow to return to initial values of donor blood stores, increase the stores, and improve the quality of erythrocyte-containing components.

Thus, it is reasonable to have ongoing monitoring over donors with an increased number of blood donations per year by a number of necessary parameters of iron exchange and borderline Hb value and take a decision regarding the increased duration of an interval between donations or regarding a limited allowable number of donations per year.

When the donor experience is increased in four and over years, the rate of LID within the group of investigated donors is progressing. This prevents iron deficiency and stores donor's health. Iron deficiency is mainly the issue

Table 3. Groups of donors of blood and (or) blood components which are more prone to the risk of iron deficiency

Groups of donors of blood and (or) blood components	Lab value
Regular male donors Donor experience: ≥ 3 years Age group:< 25 and over 45 years	Donations: ≥ 6 HGB > 130 g/l SI ≤ 9.0 μM/l; SF ≤ 29.0 μg/l
Regular male donors Donor experience: ≥ 4 years Age: 25–45 years	HGB > 130 g/l Donations: ≥ 10 SI ≤ 9.0 μM/l; SF ≤ 29.0 μg/l
Female donors who gave their blood 1-2 times a year Age: 18–25 years	Donations: ≥ 2 HGB > 120 g/l SI ≤ 9.0 μM/l; SF ≤ 20.0 μg/l
Female donors mixed donations Age: 18–25 years	Donations: ≥ 6 HGB > 120 g/l SI ≤ 12.0 μM/l; SF ≤ 19.0 μg/l
Female donors thrombocytapheresis Age: over 45 years	Donations: ≥ 10 HGB > 120 g/l SI ≤ 9.0 μM/l; SF ≤ 19.0 μg/l

Table 4. Preventive activities reducing the risk of iron deficiency

Donors at risk of LID	Strategy of reducing the risk of iron deficiency in donors
Donors aged < 25 years Donors with frequent donations (> 3 times per year for males and > 2 per year for females) Donors with Hb values close to the lower limit of normal (within 135 g/l for males and 125 g/l for females) Donors with ferritin values below the reference range are ≤ 20 μg/l for females and ≤ 30 μg/l for males	1. Increased interval between donations (for instance, ≥ 6 months if no iron preparations are taken) 2. Measurement of ferritin as the basis for the motivation of donors to an independent increase of intervals between donations or recommendation of iron preparations

of nutrition. Thus, an adequate and balanced diet at any age constitutes primary prevention of iron deficiency conditions and latent iron deficiency. It is important to diagnose iron deficiency even in the lack of clinical signs, inform donors of consequences and select an optimal drug in every case by using the personalized approach [20, 21]. It is necessary to develop new programs of rational diagnostics and prevention of iron deficiency by using drugs with high effectiveness and good tolerance, which allow to replenish iron stores in LID. Preventive activities for depleted iron stores allow to preserve health of donors and reduce the rate of exemption of donors from donation in repeated blood donations and, thus, to preserve donor potential.

CONCLUSIONS

The conducted studies confirm that the complex assessment of iron exchange is necessary during the first medical examination of donors to allow for access to blood and blood component donation in order to detect latent iron deficiency and preserve health. Timely detection of latent signs of iron deficiency and risk factors of anemia belong to the most important aspect. Donors with multiple blood donations require to assess the processes of iron exchange as the rate of LID increases. As the issue of iron deficiency in donors is pressing, assessment of Hb level and introduction of serum ferritin study into the extensive practice of donorship can be of a great preventive value.

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