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## ORIGINAL ARTICLE

# Iron Store of Repeat Plasma and Platelet Apheresis Donors

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**SUMMARY**

***Background:*** **Repeat apheresis donation causes a noticeable loss of whole blood: through routine blood tests with every donation as well as through residual blood left within the used apheresis set. While the effect of blood loss on donor iron stores has been widely researched for whole blood donations, fewer and especially contradictory results exist for apheresis donors.**

***Methods:*** **A retrospective analysis of the donor blood samples (Department of Transfusion Medicine, University Hospital Erlangen) of the past 11 years (n = 52.976) was performed. Serum ferritin and hemoglobin were used to detect iron deficiency. Values at admission were compared to values measured at the donations. To investigate the impact of the donation frequency, this frequency was calculated for every single donor (for the whole duration of 11 years as well as for each individual year). Correlation and regression analyses between frequency and iron parameters were performed. A special group were long-time repeat donors, whose changes in ferritin values were analyzed in comparison to the first-ever ferritin value before the first donation.**

***Results:*** **All donor groups show significantly lower mean ferritin and hemoglobin values after repeated donations than at admission. Interestingly, there are much more iron-depleted females in the control group than there are iron-depleted males. The correlation and regression analysis showed a significant relationship between donation frequency and iron-deficiency in males, but not in females. The analysis of the long-time repeat donors showed that the relative ferritin value dropped more in males than in females. When comparing iron-depleted long-time donors, females tend to be iron-depleted much more often even before the first donation.**

***Conclusions:*** **Repeat apheresis donation has a noticeable effect on the iron store of the blood donor, leading to a high percentage of iron-deficient donors, especially in women. The very small correlation between donation frequency and iron depletion for females is most likely due to the fact that women tend to be iron-deficient even before the first donation. Because of the natural variation of inter-donation-intervals, the calculated donation frequency might not be that exact. As a result, the correlation between donation frequency and iron stores might be higher than suggested by this work.**

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**KEY WORDS**

iron, iron deficiency, apheresis, blood donation, blood donor

**LIST OF ABBREVIATIONS**

Hb - hemoglobin

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## INTRODUCTION

Iron is an essential micronutrient. As the central atom of hemoglobin and myoglobin, it plays an important part in oxygen transport. Furthermore, it is a part of many enzymes, for example in the center of cytochrome P450 proteins. It is stored inside cells, mainly mucosal cells of the small intestine, bone marrow, and hepatocytes, and as ferritin, a complex of iron and the protein apoferritin. Due to a positive correlation, the iron store can be verified by determining the serum ferritin value. An absolute iron deficiency can be diagnosed with ferritin values below 15 - 22 µg/L, a latent iron deficiency with ferritin values below 40 µg/L [1-3].

Chronic iron deficiency leads to reduced synthesis of hemoglobin and thereby to anemia, which can cause deterioration of performance, reduced concentration, fatigue, dyspnea or syncope. However, even without manifest anemia, women were prone to fatigue, loss of power (both mentally and bodily) [4], and responded positively to treatment with iron substitutes [5-7].

Whereas the effect of (repeated) whole blood donation on the body and on the iron stores have been extensively studied [8-11], the question of the effect of repeated and long-term donation via apheresis has only recently arisen. According to Duggan F et al. [12], platelet donors have lower ferritin values and show higher rates of iron deficiency when donating frequently [13-15]. One group showed that apheresis donors have higher rates of iron deficiency than people who do not donate blood [3]. Two other studies did not show a significantly higher prevalence of iron deficiency of regular apheresis donors [16,17]. As many of these studies included only a small number of cases ($45 < n < 600$), further research is necessary.

### Legal basis

According to the German guidelines (Scientific Advisory Board of the German Medical Association and the Paul Ehrlich Institute), one donor is allowed to donate plasma up to sixty times per year, with a minimum interval of two donation-free days [18]. If the donor donates blood cells as well (platelets maximum 26 times a year, whole blood maximum 6 times for males and 4 times for females), the total amount of allowed donations diminishes accordingly [18].

In our donation center, we require a minimum interval of seven days between two plasma donations and of fourteen days between two platelet donations. At every donation, a certain amount of blood is drawn prior to donation start, to allow for testing of infections, blood count, etc. This loss of blood adds up over the year, leading to a maximum loss of 2.297 L of blood for plasmapheresis, 1.988 L for plateletpheresis and 3.142 L for alternating plasma- and plateletpheresis, when the maximum allowed amount of donations is undertaken. In comparison, whole blood donors lose 3.251 L (males) or 2.251 L (females) every year (testing and donation combined).

### Aim of study

As can be seen above, if an apheresis donor fulfills the legally allowed amount of donations per year, he loses a relevant amount of blood in addition to the donated blood. For women, the total amount of blood drawn for laboratory testing in apheresis donations can be higher than the allowed amount of whole blood donation.

Therefore, we sought to determine the degree to which regular and frequent apheresis donations lead to diminished iron stores of the donors. The effect of donation frequency, which has been previously tested for plasmapheresis [14] and whole blood donation [19] was further investigated. A special emphasis was given to women of childbearing age, who are considered especially vulnerable for iron deficiency [20,21].

## MATERIALS AND METHODS

A retrospective analysis of the donor blood samples (Department of Transfusion Medicine, University Hospital Erlangen) covering 11 years (2006 - 2016, n = 52.976) was performed. Donors were organized into groups, depending on the type of donations: whole blood, plasmapheresis, plateletpheresis (see Table 1). All donors had to comply with the official guidelines for blood donation [18], once before the first donation and also at every single following donation. If the donors did not meet the required criteria, a donation break was enforced (minimum 4 weeks). A control check of the conspicuous value was performed before the donor was allowed to donate blood again. This procedure allowed for the comparison of first-time donors and repeat donors.

The donation procedure was performed according to local guidelines, which adhere to the official guidelines [18].

Serum ferritin and hemoglobin were used to detect iron deficiency. Values at admission were compared to values measured at the donations. Hemoglobin was determined at every donation, while ferritin values were determined every six months.

### Type of donation

Plasma- and plateletpheresis use a single needle, one-time disposable system, thereby making the transmission of diseases from one donor of another impossible. Blood flows from the donor into the collection unit and is centrifuged to separate plasma and blood cells. Depending on the type of donation, platelets and/or plasma are collected in the collection bag while the other blood cells as well as the largest portion of plasma are returned to the donor. This process is repeated until the target quantity is collected. The donation time varies with the target quantity, usually 30 to 60 minutes for plasmapheresis and 45 to 90 minutes for plateletpheresis.

For whole blood donation, 450 mg of whole blood are taken into a special plastic bag, which usually takes 5 to 10 minutes. The clotting cascade is blocked due to the

presence of citrate inside this bag. After disconnection from the donor, the blood is processed further.

**Donors**

A total of 51,741 blood samples taken from 4,962 donors, were analyzed. This included 2,370 (47.7%) male and 2,592 (51.9%) female donors. Male donors accounted for 60.9% of the donations compared to 39.1% from female donors. The youngest donor was 18 years old, the oldest 74 years.

The donors were organized into groups (see Table 1) according to the type of donation, to allow for further comparison. A special comparison was performed for women (only two groups: apheresis donors and controls). According to Takahashi TA et al. [22], women between 18 and 50 years of age were considered to be of childbearing age.

A random sample of 543 donors (291 male and 252 female) was used to detect the prevalence of iron substitution: 2 male (0.7%) and 6 female (2.4%) donors stated that they took iron supplements.

As a special group, we investigated long-time repeat donors (n = 63, 50 male and 13 female), who had undertaken at least 60 donations within three years, with a maximum break in between two donations of 30 days. The changes in their ferritin values were analyzed in comparison to the first-ever measured ferritin value before the first donation.

**Materials**

Plasmapheresis was performed with the PCS2 (Haemonetics, Braintree, MA, USA), plateletpheresis with either Trima Accel (Terumo BCT, Lakewood, CO, USA) or Fenwal Amicus (Fresenius Kabi, Bad Homburg, Germany). The blood count, including hemoglobin, was performed using the Sysmex K 4500 (TAO Medical, Kobe, Japan). Immunoturbidimetric measurement of ferritin values was done with the AU 680 (Beckman Coulter, Brea, CA, USA).

**Statistical analysis**

Statistical analysis as well as graphic presentation of data was performed by SPSS Version 21 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA). Data were analyzed for normal Gaussian distribution by Kolmogorov-Smirnov test, significance values were calculated by Mann-Whitney U test and Kruskal-Wallis one-way analysis of variance. p-values with $p < 0.05$ were considered as significant. Testing for correlation was performed using Spearman's rank correlation coefficient ('r'), followed by analysis of regression for dependent and independent variables.

To investigate the impact of the donation frequency, this frequency was calculated for every single donor (for the whole duration of 11 years as well as for each individual year), and correlation and regression analyses between frequency and iron parameters were performed.

## RESULTS

The mean hemoglobin and ferritin values can be seen in Table 2. Significant differences ($p < 0.05$) regarding the admission values were found in the male erythrocyte donor group.

Highly significant differences ($p < 0.005$) were found in both apheresis groups as well as the mixed group (male).

**Iron deficiency**

The threshold values for absolute and latent iron deficiency vary. We therefore used two different models to check our donors for laboratory iron deficiency:

Model 1 defines absolute iron deficiency as ferritin values below 22 µg/L and latent iron deficiency with ferritin values between 22 µg/L and 40 µg/L.

Model 2 defines absolute iron deficiency as ferritin values below 12 µg/L and latent iron deficiency with ferritin values between 12 µg/L and 30 µg/L.

The standard operating procedure of our blood donation center requires ferritin levels above 10 µg/L for females and above 20 µg/L for males.

According to Model 1, 34% of female apheresis donors and 32.4% of our female control group are iron deficient, whereas only 7.9% of female apheresis donors and 9.2% of the female control group are iron deficient when regarding the second model (see Tables 4 and 5).

Male donors are iron deficient, according to Model 1, in 1.2% erythrocyte donors, compared to 2.6% at admission and 16.9% apheresis donors compared to 3.5% at admission. When regarding Model 2, 0.0% of male erythrocyte donors compared to 0.9% at admission and 1.1% of male apheresis donors compared to 0.6% at admission are iron deficient (see Tables 4 and 5).

Anemia, as the cardinal sign of iron deficiency, was analyzed using the WHO thresholds (below 130 g/L in males and 120 g/L in females) [23]. Female donors show anemia in 2.8% at admission and in 1.5% within the apheresis group. Male donors in the erythrocyte donor group show no anemia (0.0%, both values). In the male apheresis group, 0.3% are anemic (both values). There was no increase in the rates of anemia after beginning of blood donation, but there was a decrease (see Table 3).

**Frequency of donation**

The frequency of donation was computed by the formula 'total amount of donations by one donor, divided by the total timespan for donations by this donor'. The lower the frequency of donation, the rarer that particular donor has donated. Donors had to donate at least twice to be included in this sub-analysis (n = 4,815). Male donors show a significant correlation ($p < 0.001$) between frequency of donation and ferritin levels (see Figure 1). For female donors, no correlation could be found ($p = 0.238$).

The general frequency of donation is prone to inaccuracy, due to the variations of the time between two dona-

**Table 1. Donor groups.**

| Group | Donation | Available blood values | Gender |
|---|---|---|---|
| Controls | never donated | at first admission | m, f |
| Erythrocyte donors | only whole blood | at first admission & every single donation | m |
| Apheresis donors | only plasma and platelets | at first admission & every single donation | m, f |
| Mixed donors | plasma, platelets, whole blood | at first admission & every single donation | m |

**The donors were retrospectively organized into the mentioned groups to allow for further comparison. m - male donors, f - female donors.**

**Table 2. Mean hemoglobin and ferritin values.**

| Gender | Donor group | Type of donation | Hemoglobin in G/L | Mean ferritin in µg/L |
|---|---|---|---|---|
| Male | control | admission | 154 | 116.56 |
| | erythrocyte | admission<br>erythrocyte donation | 154<br>152 | 125.94<br>98.38 |
| | apheresis | admission<br>apheresis donation | 152<br>147 | 102.91<br>48.07 |
| | mixed | admission<br>erythrocyte donation<br>apheresis donation | 155<br>152<br>149 | 107.47<br>87.50<br>44.75 |
| Female | control | admission | 134 | 34.70 |
| | apheresis | admission<br>apheresis donation | 134<br>132 | 35.73<br>30.99 |

**Mean hemoglobin and ferritin values, divided by donors' gender and donor group.**

**Table 3. Hemoglobin.**

| Gender | Group | Hb in G/L | Percentage (%) | | |
|---|---|---|---|---|---|
| | | | at admission | erythrocyte donations | apheresis donations |
| Female | apheresis | < 120<br>> 120 | 2.8<br>97.2 | | 1.5<br>98.5 |
| Male | erythrocyte | < 130<br>> 130 | 0.0<br>100.0 | 0.0<br>100.0 | |
| | apheresis | < 130<br>> 130 | 0.3<br>99.7 | | 0.3<br>99.7 |
| | mixed | < 130<br>> 130 | 0.0<br>100.0 | 0.3<br>99.7 | 0.0<br>100.0 |

**Percentage of anemic donors, based on the WHO model with hemoglobin thresholds of 130 g/L in males and 120 g/L in females.**

tions and to the sometimes very long time of donation activity. Therefore, no further statistical evaluation was done. We sought to skirt this problem with a special sub-analysis, computing the frequency of donations for individual years of donation (total amount of donations in one legal year, divided by 365). As before, male donors show a significant correlation ($p < 0.001$), but females show a significance as well ($p = 0.003$).

**Table 4. Anemia, according to model 1.**

| Gender | Group | Ferritin in µ/L | Percentage (%) | | |
|---|---|---|---|---|---|
| | | | at admission | erythrocyte donations | apheresis donations |
| Female | apheresis | ferritin < 22<br>22 < ferritin < 40<br>ferritin > 40 | 32.4<br>36.3<br>31.3 | | 34.0<br>43.4<br>22.6 |
| Male | erythrocyte | ferritin < 22<br>22 < ferritin < 40<br>ferritin > 40 | 2.6<br>6.1<br>91.2 | 1.2<br>8.3<br>90.5 | |
| | apheresis | ferritin < 22<br>22 < ferritin < 40<br>ferritin > 40 | 3.5<br>12.6<br>83.9 | | 16.9<br>35.6<br>47.5 |
| | mixed | ferritin < 22<br>22 < ferritin < 40<br>ferritin > 40 | 2.0<br>5.3<br>92.7 | 3.1<br>14.7<br>82.2 | 17.9<br>35.3<br>46.8 |

**Percentage of anemic donors, based on model 1 with a ferritin threshold of 40 µg/L. Absolute iron deficiency is defined as ferritin values below 22 µg/L and latent iron deficiency with ferritin values between 22 µg/L and 40 µg/L.**

**Table 5. Anemia, according to model 2.**

| Gender | Group | Ferritin in µ/L | Percentage (%) | | |
|---|---|---|---|---|---|
| | | | at admission | erythrocyte donations | apheresis donations |
| Female | apheresis | ferritin < 12<br>12 < ferritin < 30<br>ferritin > 30 | 9.2<br>40.2<br>50.5 | | 7.9<br>51.1<br>41.0 |
| Male | erythrocyte | ferritin < 12<br>12 < ferritin < 30<br>ferritin > 30 | 0.9<br>2.6<br>96.5 | 0.0<br>3.0<br>97.0 | |
| | apheresis | ferritin < 12<br>12 < ferritin < 30<br>ferritin > 30 | 0.6<br>7.9<br>91.5 | | 1.1<br>33.8<br>65.2 |
| | mixed | ferritin < 12<br>12 < ferritin < 30<br>ferritin > 30 | 0.6<br>2.8<br>96.7 | 0.0<br>8.5<br>91.5 | 2.8<br>31.0<br>66.2 |

**Percentage of anemic donors, based on model 2 with a ferritin threshold of 30 µg/L. Absolute iron deficiency is defined as ferritin values below 12 µg/L and latent iron deficiency with ferritin values between 12 µg/L and 30 µg/L.**

In the regression analysis, no influence of the donation frequency per year on the ferritin value was found for women ($F = 0.007$, $p = 0.933$). For men, an influence was found (apheresis group: $F = 151.077$, $p < 0.001$, mixed group: $F = 49.042$, $p < 0.001$).

A significant correlation was found for the frequency of donation per year and the hemoglobin (male: apheresis group: $r = 0.054$, mixed group: $r = 0.053$, both $p < 0.001$; female: $r = 0.053$, $p < 0.001$). In the regression analysis, a fundamental impact was found (male: apheresis group: $F = 32.46$, $p < 0.001$, mixed group: $F = 11.39$, $p < 0.005$; female: $F = 56.73$, $p < 0.001$).

**Women of childbearing age**

A special group that drew a lot of interest in our hypothesis were women of childbearing age. But whether we defined the childbearing age to end at 50 years or at 40 years, the results did not differ from the general female results mentioned above.

**Long time donors**

Another special group were long time donors. These were defined as donors who (i) had been donating for at least three years, (ii) had donated at least 60 times in these three years, and (iii) had donated at least every 30

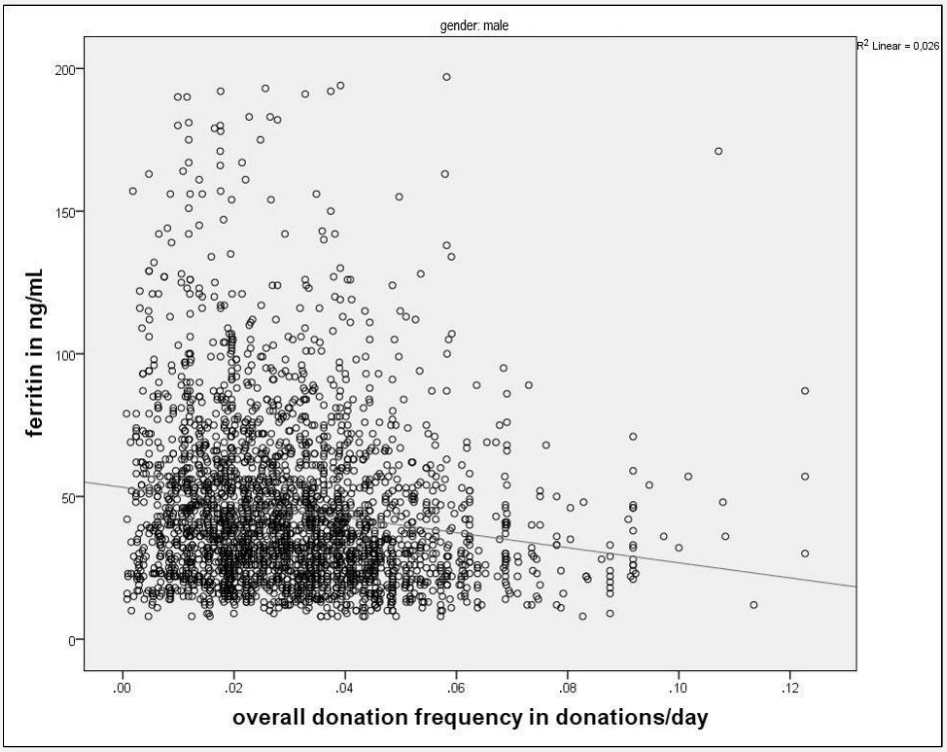


**Figure 1. Correlation of donation frequency and ferritin.**

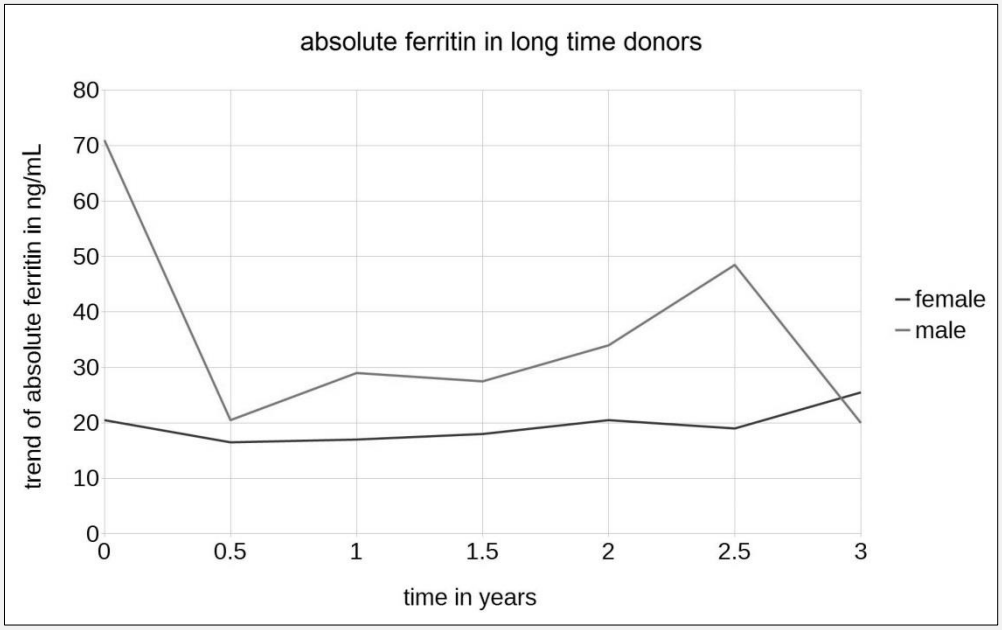


**Figure 2. Absolute ferritin in long time donors.**

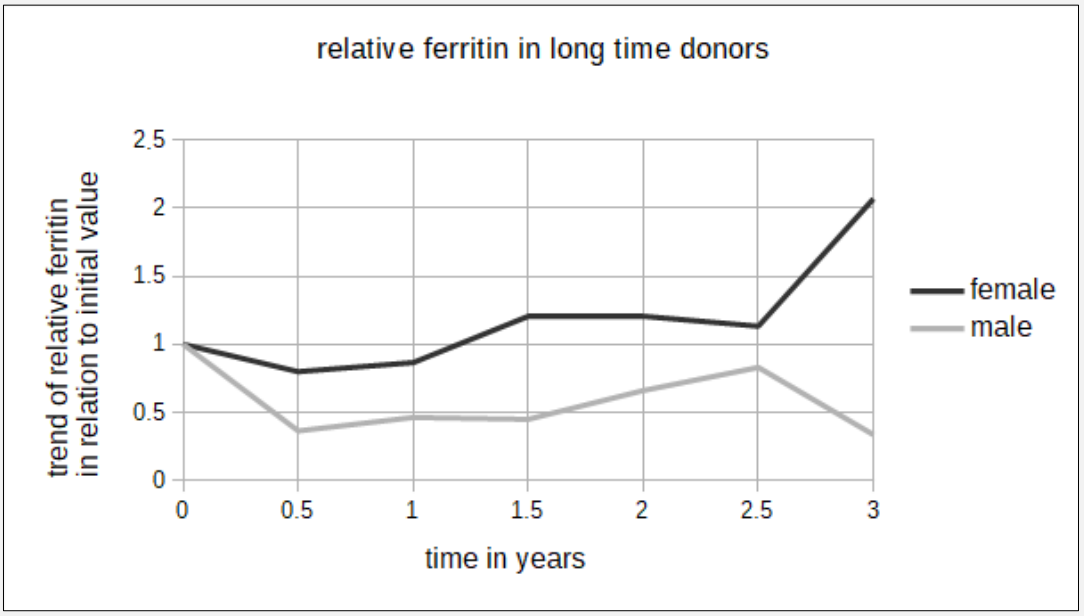


**Figure 3. Relative ferritin in long time donors.**

days. The absolute ferritin values can be seen in Figure 2. Additionally, the ferritin values were compared to the ferritin values at admission. These relative ferritin values can be seen in Figure 3.

These long-time donors were further analyzed for iron deficiency. Women showed higher levels of iron deficiency from the beginning with no relevant increase after three years: 69.2% of our female long-time donors were iron deficient at admission and 77.7% after three years.

But while only 46% of our male donors were iron deficient at admission, after three years of regular donation they had almost caught up to the female donors with an iron deficiency prevalence of 68.2%.

**Correlation of body weight with iron storage**

Hemoglobin and body weight showed a significant correlation in the apheresis group (male $r = 0.026$, $p < 0.001$ and female $r = 0.067$, $p < 0.001$) and in the mixed group (male $r = 0.095$, $p < 0.001$). No correlation was found at admission and in the erythrocyte donor group. A significant correlation of ferritin at admission and body weight was found (male $r = 0.205$, $p < 0.001$ and female $r = 0.150$, $p < 0.001$). No correlation could be found for the other different donation groups.

**Donor suspension**

Out of all donations analyzed, 14,472 temporary suspensions were found. In male donors, 21.1% (n = 8,444) of suspensions were due to low hemoglobin or ferritin values. In comparison, these accounted for 50.1% (n = 6,028) of suspensions in female donors.

Suspensions due to low ferritin can be found approximately equally often in both genders (male 12.5%, female 10.9%). Suspensions due to low hemoglobin are much more often found in women (n = 2,362, 39.2%) than in men (n = 726, 8.6%), thereby being responsible for the above-mentioned difference between males and females.

## DISCUSSION

We aimed to determine the effect of repeat apheresis donation on the donor's iron storage, with a special emphasis on women of childbearing age, by analyzing ten years of routine donor data from our donation center. Both hemoglobin and ferritin were significantly lower after donations, the percentage of iron depleted donors was higher in all groups after donations than at admission. For male donors, a weak negative correlation was found between donation frequency and hemoglobin as well as ferritin. This shows that repeat apheresis donation has a negative effect on the donor's iron storage, mostly due to blood samples for testing and residual blood in the one-time donation set, which are lost at every single donation. The results for women are less pronounced than for men, but since they show a markedly

lower ferritin value at admission, we interpret these findings to show a high risk of iron deficiency for repeat female donors. We conclude as well that this group must have effective compensation mechanisms for the loss of iron, either through nutrition or through iron supplementation.

Since our donors undergo routine hemoglobin testing at every single donation and since 1997 ferritin testing at least every six months (routinely recommended by now [24]), there is no acute risk for anemia. Donors, who fail to meet our criteria, are excluded from donating for a certain amount of time and are provided with iron supplements. For safety reasons, our hemoglobin limits are 5 g/L higher than in the WHO anemia definition [23]. According to WHO criteria, 1.5% of our female donors and a maximum of 0.3% of our male donors are temporarily anemic. These findings are lower than the WHO findings for anemia in the European population (women (15 to 59 years) 10.3%, men (15 to 59 years) 4.5% [25]) and shows that our prevention strategies for donor anemia are effective.

Our findings are surprisingly consistent with other, older studies regarding the iron stores of whole blood donors [8,9]. Generally, blood donation via apheresis is held to have less effect on the donor's hemoglobin and iron store. We showed that this is not the case, especially if the donor exhausts the officially allowed amount of donations per year. The cumulative blood loss, through donations, residual blood in the one-time donation set, and blood drawn for laboratory testing, adds up to a relevant amount and can lead to iron depletion of the donor.

The major weakness of our study is the retrospective design, which sometimes leads to vague results. In addition, information regarding menstruation or symptoms associated with iron deficiency are missing. All we asked was "are you feeling unwell or are you on sick leave", which lead to donor deferral for the time being. The variation of the time between individual donations reduces the informative value of the donation frequency results.

## CONCLUSION

Repeat apheresis donation has a noticeable effect on the iron store of the donor, leading to a high percentage of iron-deficient donors, especially in women. The very small correlation between donation frequency and iron depletion for females is most likely due to the fact that women tend to be iron-deficient even before the first donation.

**Declaration of Interest:**
None.

**Source of Funds:**
No involvement of a pharmaceutical company.

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