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Pilot Study to Gain First Indications for the Impact of a 3-Month's Oral Intake of a Sucrosomial Iron Supplement on Hemoglobin in Iron-Deficient Blood Donors

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Keywords
Sucrosomial iron · Blood donors · Iron deficiency · Oral iron intake

Abstract
Introduction: Regular whole blood donors often suffer from iron deficiency (ID) or iron deficiency anemia due to the loss of 200–300 mg of iron with each donation. Hemoglobin (Hb) as donor eligibility criterion reflects iron stores only poorly. ID in blood donors is typically prevented or treated with orally administered ferrous salts, which frequently cause gastrointestinal side effects. A high daily oral iron dose is counterproductive due to hepcidin upregulation. Oral sucrosomial iron ($_{sucr}$iron) is encapsulated ferric pyrophosphate that may be an option for blood donors due to its supposed high bioavailability and good tolerability. ***Methods:*** This monocentric single-cohort pilot study included fifty whole blood donors (divided into premenopausal women, postmenopausal women, and men) who did not meet Hb donation criteria. Participants aged 18–65 years with ferritin <30 ng/mL and venous Hb <12.5 g/dL in women and Hb <13.5 g/dL in men received oral $_{sucr}$iron (30 mg iron) for 90–120 days. Primary endpoints were the increase of Hb and ferritin. ***Results:*** Forty-seven participants completed the study. With the limitation that no control group was included, there was a substantial overall median increase of 0.94 g/dL Hb and 4.97 ng/mL ferritin (standardized on 90 days of iron intake). These value improvements were likewise observed in each of the subgroups. $_{sucr}$iron was very well tolerated, with almost no gastrointestinal side effects identified. ***Conclusion:*** A clear increase of Hb and ferritin was observed after the intake of $_{sucr}$iron, so it may be a reasonable and useful alternative to traditional oral iron therapy. The ease of administration, pleasant taste, dietary supplement status, and, most importantly, good tolerability highlight the value of $_{sucr}$iron supplementation.

Introduction

Human blood is a crucial element of public health. A sufficient supply of blood products is intrinsically connected to the viability of numerous progressively complex medical and surgical procedures. Therefore, blood and its derivates are included in the World Health Organization's model list of essential medicines [1]. Donation centers have a bidirectional responsibility to maintain adequate blood supply for patients while also caring for the health of donors. As a result of this responsibility, there is a continuous requirement to safeguard blood donors' long-term health. A whole blood donation of 450–500 mL results in a loss of 200–300 mg iron whereas daily average iron resorption is 1–2 mg [2, 3]. Therefore, iron deficiency (ID) and iron deficiency anemia (IDA) are commonly reported in regular blood donors, with a rate of up to 50% in male and up to 75% in female donors [4]. Kiss et al. [5]

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showed that within 168 days after a whole blood donation, 67% of untreated iron-deficient donors were unable to recover iron. Female gender, low body weight, and a high donation frequency are aggravating factors in the failure to restore iron balance [6, 7]. In Styria, donor eligibility criteria include a point-of-care test (POCT) for hemoglobin (Hb) using capillary blood from a fingerstick sample. Lower Hb donation thresholds are 12.5 g/dL for women and 13.5 g/dL for men. However, Hb levels do not accurately reflect body iron stores because IDA is a late consequence of ID [8]. As a result, even if their Hb levels meet donation guidelines, donors may be iron deficient and are at danger of further decreasing their iron stores. ID occurs when any loss of iron cannot be compensated for by diet [9] and is associated with symptoms such as chronic fatigue syndrome, decreased cognitive and physical performance, sleeping disorders, and restless legs syndrome (RLS) [10, 11]. Iron has been substituted orally for decades as ferrous sulfates, citrates, and fumarates. When ferrous salts are used, daily doses are limited due to the upregulation of hepcidin and associated inhibition of iron absorption [12, 13]. Consequently, conventional iron substitution has recently been recommended in either low doses or every other day [13]. Patients' adherence is low due to the long duration of therapy and intake modalities, as well as often-reported gastrointestinal side effects, resulting in therapy cessation and insufficient iron recovery. A promising new oral sucrosomial iron ($_{sucr}$iron), consisting of ferric pyrophosphate encapsulated in sucrosomes through a phospholipid bilayer membrane, is stated to be highly bioavailable, well tolerated, and easy to use. Preclinical data have shown that $_{sucr}$iron preparations pass through the stomach unmodified, avoiding direct irritation of the gastric mucosa, which is frequent with other oral iron formulations. Iron is subsequently released directly in duodenum, allowing iron ions to be transported across the intestinal epithelium without the assistance of divalent-metal transporter 1 [14, 15]. Microfold cells of Peyer's patches in the small intestine allow absorption where macrophages transport iron into the lymphatic system [15]. $_{sucr}$iron supplementation has successfully been tested on patients with chronic renal failure [16], pregnant women without anemia [17], anemic cancer patients [18], patients who are intolerant and/or refractory to iron sulfate [19], and celiac patients [20]. In Austria, $_{sucr}$iron has the status of a food supplement. In this descriptive explorative pilot study, we aimed to obtain first data on the effects of $_{sucr}$iron on Hb and ferritin concentrations in iron-deficient whole blood donors. Additionally, we investigated the acceptability and tolerability of a three-monthly oral intake of the study product and gathered data on symptoms that may be related with ID.

Materials and Methods

Study Design

This monocentric single cohort study in an interventional setting is classified as food study. Recruitment began in November 2019 and ended in June 2020. The study included 50 whole blood donors who had been rejected from blood donation due to low capillary POCT Hb levels (Hb <12.5 g/dL in women and Hb <13.5 g/dL in men). At the blood drive, these donors are routinely offered the opportunity to have their Hb and ferritin levels analyzed at the Department of Blood Group Serology and Transfusion Medicine. These results were taken as the study's baseline values. Further requirements were ferritin levels less than 30 ng/mL and a time period of more than 2 months between the previous whole blood donation and current Hb values. For both men and women, the minimum inter-donation interval for two whole blood donations is 8 weeks. Except for the Hb value, donors had to meet Austrian blood donation requirements and range in age from 18 to 65 years. Donors who met the inclusion criteria for Hb and ferritin were queried for exclusion criteria and invited to participate by phone. Exclusion criteria included pregnancy and lactation, chronic diarrhea, fructose intolerance or any other incompatibilities with the product's contents, as well as iron supplementation during the previous 3 months. The first visit (V1) on day 0 was scheduled within 21 days following blood collection and included the recording of relevant pre-existing medical conditions and/or therapies, as well as the initial completion of the prepared questionnaires. At V1, the participants were given four boxes $_{sucr}$iron, each containing 30 sachets. The last assessment (V2) and conclusion of the participation was scheduled 90 days after V1, on day 90, with a tolerance of 30 days, resulting in an observational period of 90–120 days. Participants had to be subjectively healthy for V2 to avoid infection-associated falsely high ferritin readings; therefore, at V1, they were instructed to postpone V2 if they became ill. At V2, they were queried regarding clinical symptoms of illness. Adverse events (AEs) associated with or unrelated to the test product, accompanying diseases, relevant medication, and potential dropout criteria, were investigated. Dropout would occur if the following conditions were met during the study period: taking fewer than 75% of the prescribed sachets, improper consumption on more than 25% of the days, administration of medication or other dietary supplements that might affect the iron balance, noncompliance with the 30 days tolerance for V2 or omission of V2, trauma or medical interventions involving blood loss or blood donation, diarrhea on more than 25% of the days, pregnancy or withdrawal of consent to study participation. Finally, blood was drawn for Hb and ferritin testing. Included primary endpoints are the increase of Hb and ferritin levels after oral intake of $_{sucr}$iron. Secondary endpoints include assessing the treatment's feasibility, as poor compliance is a major issue with conventional oral iron, as well as the tolerability and safety of the study product by assessing the occurrence of any symptoms related or possibly related to the study product's intake (AEs and serious adverse events). Following V2, a written report with the results and any recommendations was sent to each participant.

Questionnaires

At V1, participants were asked to fill out a questionnaire including any relevant preexisting medical conditions, information on previous iron intake and related AEs, as well as dietary habits. At V2, AEs associated with or unrelated to the test product, accompanying diseases, relevant medication, and potential dropout criteria, were investigated. They were also asked to offer details and score their experience with the $_{sucr}$iron. At each visit, possible clinical symptoms of ID were assessed using validated questionnaires

Table 1. Characteristics of participants consuming at least 3 months of iron supplementation (per protocol) at V1

Characteristic	PrW	PoW	Men	Overall *p* value
n (%), total 47	23 (48.9)	10 (21.3)	14 (29.8)	–
Age, mean (SD), years	36.99 (11.21)	48.95 (11.38)	47.98 (12.91)	0.006[a]
Height, mean (SD), cm	167.13 (5.93)	163.20 (7.27)	178.50 (8.54)	<0.001[b]
Weight, mean (SD), kg	64.57 (8.91)	65.1 (13.82)	80.57 (17.9)	0.003[c]
BMI, mean (SD), kg/m^2	23.16 (3.37)	24.42 (4.52)	25.12 (4.28)	0.202
Vegetarian/vegan, yes/no	3/20	0/10	0/14	0.242
Dietary habits, *n* (%)				Sum
Meat 5-6x per week	4 (20)	1 (10)	6 (42.9)	11
Meat 3-4x per week	9 (45)	2 (20)	6 (42.9)	17
Meat 1-2x per week	7 (35)	7 (70)	2 (14.3)	16
Preference in meat type				
None, *n* (%)	14 (70)	6 (60)	10 (71.4)	30
White meat, *n* (%)	3 (15)	2 (20)	2 (14.3)	7
Red meat, *n* (%)t	3 (15)	1 (10)	2 (14.3)	6
History of anemia	15 (65.2)	5 (50)	11 (78.6)	31
History of oral iron intake	12 (52.2)	3 (30)	5 (35.7)	20

The table contains information on dietary habits, including the frequency of meat consumption per week and meat type preferences, as well as on historical data on anemia and previous conventional oral iron intake. BMI, body mass index; SD, standard deviation. [a] $p < 0.05$ for PrW versus PoW and PrW versus men. [b] $p < 0.05$ for PrW versus men and PoW versus men and [c] $p < 0.05$ for PrW versus men and PoW versus men.

for RLS [21], fatigue [22, 23], sleep [24], and quality of life [25]. For more detailed information, see online supplementary 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000527577).

Laboratory Tests

Laboratory tests were performed at the time of blood donation deferral and at V2. Venous Hb was measured from EDTA blood by cyan methemoglobin method (Advia® 2120/120, Siemens Healthcare Diagnostics, Siemens AG Vienna, Austria), and ferritin was measured from serum using a chemiluminescence immunoassay (Laison® Ferritin, Liaison® XL; DiaSorin S.p.A., Saluggia, Italy), both according to manufacturers' instructions.

Treatment

At V1, donors were given oral $_{sucr}$iron (OLEOvital® EISEN FORTE; PharmaNutra S.p.A., Pisa, Italy, licensed by Fresenius Kabi Austria GmbH, Graz, Austria), containing 30 mg of iron and 70 mg vitamin C. The study product had to be taken daily, regardless of daytime or concurrent use of medication, food, or beverages, for 90–120 days equating to 2,700–3,600 mg iron. The dosage prescribed was in accordance with the manufacturer's recommendations for use.

Statistical Analysis

Before comparing premenopausal women (PrW) versus postmenopausal women (PoW) versus men, all data of continuous variables were checked for normal distribution (test of normality: Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%) and for heteroscedasticity (Levene test, type I error = 5%). As none of the variables presented in this paper showed data sets with both normal distribution and homoscedasticity, all comparisons were performed by a nonparametric analysis of variance (Kruskal-Wallis test, followed by Nemenyi's multiple comparisons). Data from the single presented categorical variable (vegetarian + vegan) were compared by the exact χ^2 test.

Pre-post-comparisons of continuous variables with normally distributed data were performed by the paired *t* test; otherwise, the exact Wilcoxon test was used. Dichotomous variables were compared by the exact McNemar test. Multiple regression analyses were used to investigate the influence of the following variables on delta hemoglobinV2-V2/90d and on delta ferritinV2-V2/90d: subgroup membership (PrW vs. PoW vs. men); Hb or ferritin, weight, age, BMI (all at baseline); RLS at baseline and at the end of iron supplementation; ratio iron prescription/iron intake; history of anemia or ID; diarrhea during iron supplementation.

Since the type I error was not adjusted for multiple testing, the results of inferential statistics are descriptive only and the use of the term "significant" in the description of the study results always reflects only a local $p < 0.05$ but no error probability below 5%. Statistical analysis was performed using the open-source R statistical software package, version 4.0.5 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Between November 2019 and June 2020, 92 eligible whole blood donors were invited to take part in the study of which 50 were enrolled. After the target number of participants was reached, recruitment was discontinued. Three study candidates had to be excluded from the statistical analysis due to protocol violations. One participant donated whole blood (PrW), one took less than 75% of the prescribed sachets (PrW) due to forgetfulness, and one man did not complete the final examination due to an active SARS-CoV-2 infection during the study interval. The remaining participants were as follows: 23 PrW,

Table 2. Results for laboratory parameters at V1 and V2 including 47 participants

Parameter	Reference range	Visit	PrW	PoW	Men	PoW and men
Hb, median (IQR), g/dL	≥12.5/≥13.5[a]	V1	12.0 (11.7, 12.2)	12.0 (11.5, 12.1)	12.5 (12.1, 13.0)	12.1 (11.6, 12.6)
		V2	12.6 (12.3, 13.5)	13.1 (12.7, 13.2)	13.6 (12.7, 14.6)	13.1 (12.7, 14.2)
p value			**<0.001**	**0.002**	**0.001**	**<0.001**
Ferritin, median (IQR), ng/mL	30–150	V1	8.3 (6.8, 10.3)	10.3 (6.3, 16.2)	10.1 (8.2, 13.8)	10.3 (7.3, 15.0)
		V2	14.5 (11.1, 17.1)	18.4 (12.5, 24.5)	16.0 (8.2, 18.8)	16.9 (12.3, 22.6)
p value			**<0.001**	**0.005**	**0.035**	**<0.001**

Hb, hemoglobin; IQR, interquartile range (25th, 75th percentile). [a] Hb values refer to eligibility criteria for donation for women and men.

10 PoW, and 14 men. Overall, the median iron sachet consumption was 97 (interquartile range: 92, 102), equivalent to 2.910 mg $_{sucr}$iron, and the 90-day ratio of prescribed sachets to sachets taken was 1.01 (interquartile range: 1.0, 1.04).

For practical reasons, the period between the first and the second examination and thus the duration of iron intake varied from 90 to 120 days. Therefore, as a result, all outcomes were standardized to 90 days by interpolation.

Characteristics of Participants

Participants' characteristics at baseline and history of ID are summarized in Table 1. A significant difference was found in age, height, and weight. This is due to the participation of both women and men, as well as the distinction between PrW and PoW. The significant difference in baseline Hb between the subgroups at V1 (p = 0.023; for values, see Table 2) is due to the inclusion of men and women, as well as the different cutoff values for admittance to blood donation.

There were only three vegetarians among the participants. Nobody reported daily meat consummation. Eleven participants eat meat 5-6 times per week, 17 3-4 times, and 16 once or twice per week. The majority of participants (30; 68.%) have no preference in meat type, while six prefer red meat and seven prefer white meat (see also Table 1).

History of anemia (for subgroups, see Table 1): thirty-one participants reported that they had previously been diagnosed with anemia. Of these, 20 had already taken conventional iron supplements in the past, of which nine had suffered from side effects (45%). The most common gastrointestinal side effects reported were constipation (3), diarrhea (2), flatulence (2), nausea (2), and gastric distention/cramps (3). The following other side effects were each named once: fatigue, headache, skin rash, itching.

Adverse Events

There were three recorded AEs. One participant had trouble falling asleep at first, another had loose stools on occasion, and one had pain in his fingers and both wrists 2 weeks after starting the iron supplements. There were no further documented side effects or AEs. The latter two incidents were reported to the manufacturer, who did not classify them as possibly caused by $_{sucr}$iron. Overall, the participants rated the $_{sucr}$iron very highly. All of them would also take it again, with the easy handling during intake, the nice flavor, and the perceived favorable effect as key reasons.

Hb and Ferritin Levels

When compared to the initial results, there is a marked increase in Hb and ferritin values, with an overall median increase of 0.94 g/dL for Hb and 4.97 ng/mL for ferritin. Men and women have similar median Hb increases (0.84, 0.99, and 0.87 g/dL for PrW, PoW, and men, respectively). The median ferritin increase within the subgroups is 5.08, 7.42, and 2.7 ng/mL for PrW, PoW, and men. Despite the fact that men had the smallest increase in ferritin, the improvement in Hb and ferritin levels was statistically conspicuous in all subgroups (Table 2; Fig. 1).

Multiple regression analyses showed that none of the examined variables had a significant effect on the increase of Hb ($\Delta_{Hb\ (V2\text{-}V2/90d)}$). However, the increase of ferritin ($\Delta_{ferritin\ (V2\text{-}V2/90d)}$) was favored by iron intake compliance (ratio iron prescription/iron intake; $p = 0.022$) and by RLS at baseline ($p = 0.036$).

ID-Associated Symptoms at V1 and V2

Table 3 shows the overall results for symptoms associated with ID. PrW experienced the most symptoms including brittle nails (V1, V2: 9 [39.1%], 6 [26.1%]), increased hair loss (V1, V2: 9 [39.1%], 5 [21.7%]), shortness of breath/palpitations (V1, V2: 8 [34.8%], 7 [30.4%]), and dizziness (V1, V2: 7 [30.4%], 6 [26.1%]). There were no reports of men experiencing increased hair loss, load-dependent headaches, or dizziness. A noticeable improvement in brittle fingernails was reported by 54.5% (95% confidence intervals [CI], 23.4–83.3) of participants, in hair loss 75.0% (95% CI, 34.9–96.8), and in shortness of breath/palpitations during exercise 55.6% (95% CI, 21.2–

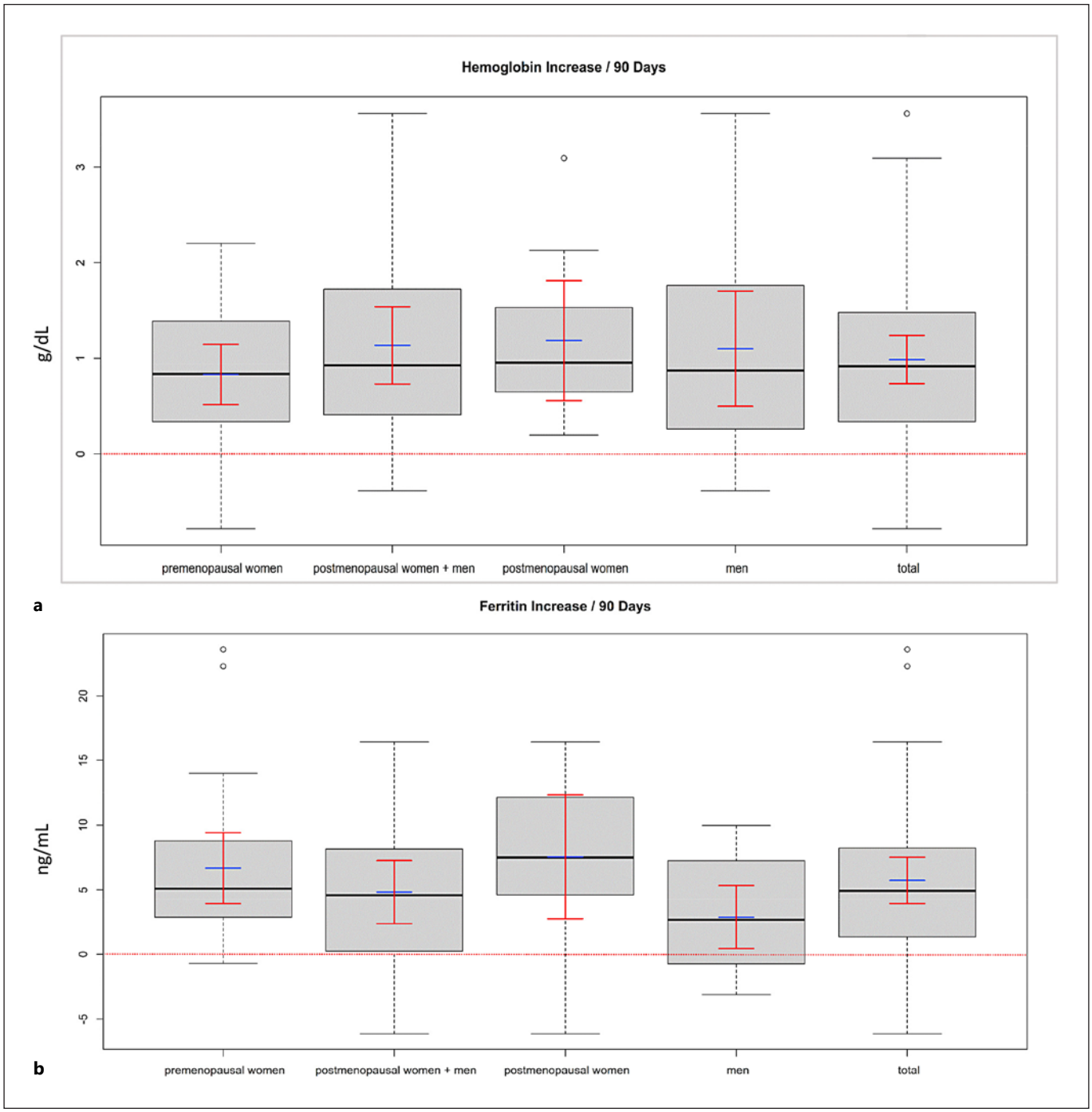

Fig. 1. Increase of Hb and ferritin in subgroups over 90 days. **a** Hb. Boxplot with black line, box, whiskers, and circles (median, interquartile range [IQR], "minimum"/"maximum," and outliers); blue line in boxes, mean; red whiskers in boxes, lower and upper limit of 95% confidence intervals (CI) for mean; red dotted line at y = 0 indicates no change. **b** Ferritin. Boxplot with black line, box, whiskers, and circles (median, IQR, "minimum"/"maximum," and outliers), blue line in boxes, mean; whiskers in boxes, lower and upper limit of 95% CI for mean; dotted line at y = 0 indicates no change.

86.3). However, the improvements were not statistically significant. Online supplementary 1 contains the findings on RLS, fatigue, sleep, and quality of life.

Discussion

In this pilot study, we found that after oral intake of $_{sucr}$iron over 90 days there was a marked increase in both, Hb and ferritin. Overall, the median increases of Hb and

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Table 3. Comparison of symptoms of all participants to ID-associated symptoms at V1 and V2

Symptoms of ID	V1, *n* (%)	V2, *n* (%)	*p* value
Brittle nails	17 (36.2)	11 (23.4)	0.109
Increased hair loss	13 (27.7)	8 (17)	0.063
Load-dependant headache	5 (10.6)	6 (12.8)	>0.999
Shortness of breath/palpitations during exercise	13 (27.7)	9 (19.1)	0.219
Dizziness	7 (14.9)	6 (12.8)	>0.999
Painful or "slippery" tongue	1 (2.1)	0	>0.999
Unexplained food/nonfood cravings (Pica)	0	1 (2.1)	>0.999

ferritin are 0.94 g/dL and 4.97 ng/mL, respectively. In a comparable study, oral administration of 30 mg of conventional iron for 3 months resulted in a mean increase in ferritin of 5.9 ng/mL in PrW with no change in mean Hb [26]. Men benefit less than women do from $_{sucr}$iron intake in terms of ferritin levels (median increase of 2.7 vs. 5.08 and 7.42 ng/mL, men, PrW, and PoW, respectively) despite comparable consumption of sachets and having approximately the same baseline values as PoW. This could be due to men having a higher erythrocyte mass (men 2,087.5 mL vs. 1,405.9 mL in women [27]), or/and skeletal muscle mass (30.6 vs. 38.4% relative to body mass of men [28]), where missing iron could have been utilized to a greater extent, leaving less storage iron. PoW appear to benefit more from iron supplementation than PrW, which seems plausible because PrW lose blood (and thus iron) through menstruation. Nevertheless, a desired ferritin threshold (30 ng/mL) was not reached, which could be resolved by increasing the dose (e.g., 60 mg) or extending the duration of $_{sucr}$iron intake.

Encouragingly, participants experienced remarkably few AEs and/or side effects associated with $_{sucr}$iron intake, although some reported complaints associated with conventional oral iron therapy in the past. It seems reasonable to attribute this to the product's favorable biochemical properties and to the low daily iron intake of only 30 mg in this trial, which is well below the commonly prescribed dosage of 100 mg of elemental iron per day. However, even at substantially lower doses of traditional iron preparations, more side effects are reported [29]. Except from one case of occasionally loose stools in the study period, no gastrointestinal AEs were documented, implying that gastrointestinal tolerance of $_{sucr}$iron appears to be excellent. This reflects the fact that all participants would be willing to take this food supplement again if ever needed. Concerning the presumed AE of pain in the joints and fingers, there is no direct or obvious link between the product's consumption and the complaints. According to manufacturer's comments, similar problems about $_{sucr}$iron supplementation had not been documented in Italy or other countries. Furthermore, only remarkably few participants had to be excluded from the study (n = 3), none of them due to AEs.

Further questions were addressed using validated questionnaires on ID symptoms: RLS, fatigue, sleep, and perception of quality of life. They are discussed in online supplementary 1.

The administration of supplements to otherwise healthy blood donors raises the question, whether such an approach is ethically justifiable. One argument against supplementation might be that treating healthy people with ID is solely masking laboratory values with unnecessary medication and possible side effects. However, we are convinced that iron administration as a preventive measure for donors with ID as a result of a voluntary medical intervention provides both immediate and long-term health benefits and may delay or avoid IDA in future blood donations. In a study with 2-year follow-up, regular blood donors with ID not receiving iron substitution (placebo group and group without any information on iron status) had a mean ferritin increase of 0.8 and 0.3 ng/mL and a mean change in venous Hb of −0.07 and −0.13 g/dL at the final visit, respectively [30]. This underscores the fact, that without additional iron consumption, recovery of iron stores in regular blood donors is poor [5]. If a greater proportion of repeat donors remain healthy, the necessary blood demand can be fulfilled by a greater number of donors, and the donation frequency per donor decreases. This in turn helps to maintain individual iron stores in this population. At this point, $_{sucr}$iron as a food supplement would be a good alternative for blood donors with practically no side effects and flexible modalities for intake (with or without meals, other medications, and at any time of day) making this supplement ideal for donors who are not accustomed to taking medication. A disadvantage is the comparatively high cost of $_{sucr}$iron, which is about ten times higher than conventional oral iron preparations and, due to its classification as a food supplement it is, at least in Austria, not generally covered by health insurances. In addition to oral iron therapy, intravenous iron substitution may also be an effective strategy to replenish iron stores. However, it is substantially more expensive, requiring a venous access as well as monitoring during infusion due to rare hypersensitivity reactions.

With our research, we would like to address the iron stores in blood donors in particular. It was interesting to

see that almost two-thirds of our participants had previously been diagnosed with IDA, and almost 65% of them had also taken iron in the past. The remaining, however, had not. The latter could imply that donors underestimate or are even unaware of the iron loss during blood donation and that they rarely feel the need to take medication without a certain level of suffering. In addition, the symptoms of ID can be ambiguous and elusive, owing in part to the gradual onset of symptoms, which is why donors believe they are healthy enough to donate despite ID. There are numerous approaches to dealing with iron storage in whole blood donors. They include Hb- or ferritin-targeted donation intervals as well as iron supplementation [31]. Nevertheless, current Austrian blood donor regulations do not explicitly address this issue [32] although an adaptation of the regulation is planned. It would be preferable to implement safeguards, such as algorithms that consider Hb, ferritin, and an individual donation frequency, to ensure that blood donors to not develop ID in the first place.

Limitations

Here, we describe the results of a single-arm pilot study. Lacking a control group, spontaneous increase of Hb levels due to naturally occurring auto-regeneration over time could have influenced the results of the study. Mujica-Coopman et al. [26] found a mean increase of 0.6 ng/mL for ferritin and even a slight decrease of −0.3 g/dL for Hb in PrW (one-third with ID of varying severity) after 3 months of placebo intake. In another study, placebo use for 3 months showed a mean change for Hb of −0.05 g/dL and for ferritin of 0.2 ng/mL in PrW with ID [33]. We therefore assume that the improvement in Hb and ferritin levels in our participants may well be attributable to the $_{sucr}$iron consumption, although at least 2,700 mg of $_{sucr}$iron were insufficient to compensate for the iron loss of a whole blood donation. In addition, the small sample size may limit the significance of our findings. $_{Sucr}$iron, like other standard oral iron treatments, contains ascorbic acid. It is unclear whether it enhanced iron bioavailability during the study interval. Although ascorbic acid is acknowledged as an iron uptake enhancer, there are also investigations that have found little effect [34]. The total benefit of vitamin C may be less pronounced because our study participants were not instructed to avoid inhibitors of iron absorption, such as tea, coffee, and dairy items; on the contrary, they were encouraged to take the sachets along with their meals. In terms of clinical symptoms, a placebo effect caused by awareness of an effective supplement could have influenced the study's results.

Overall, the observed increases in outcomes can be understand as trends and indicators of therapeutic success. However, we believe that these findings, along with those from other studies on the use of $_{sucr}$iron administration that included participants with diseases or other physical circumstances, are compelling enough to merit follow-up research. A confirmatory study would have to be conducted with a reasonable number of participants based on sample size estimation, and would have to be double blinded and placebo controlled, using an iron dose of at least 60 mg per day or a comparison of 30 mg per day with 60 mg per day. A comparison group could also receive ascorbic acid. Other iron characteristics that should be examined include transferrin saturation, soluble transferrin receptor, and hepcidin as a critical regulator of iron homeostasis [35].

Strengths of the Study

To our knowledge, this is the first study of $_{sucr}$iron administration in healthy blood donors with ID or IDA who do not have any other major health concerns.

Conclusion

ID and IDA can result in the loss of blood donors who cannot be readmitted to blood donation unless iron supplements are taken. $_{sucr}$iron might be a good alternative to conventional iron therapy, especially for a population that takes little medicine, such as blood donors. The ease of use, the pleasant taste, the status of a food supplement in Austria, and, most importantly, the low occurrence of side effect are all facts in its favor. Overall, it appears to be effective; however, this would need to be confirmed in a detailed follow-up study with higher dosage or an expansion of the administration time.

Statement of Ethics

The Ethical Committee of the Medical University of Graz approved the study (31-435 ex 18/19). It was carried out under GCP guidelines and the Declaration of Helsinki. Furthermore, it was registered at ClinicalTrials.gov (NCT04250298). At the initial visit (V1), participants gave written informed consent to participate in the study.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest relevant to the manuscript.

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Author Contributions

Camilla Drexler-Helmberg, Patrick Paul Torreiter, Peter Schlenke, Petra Krakowitzky, Wolfgang Schimetta, and Wolfgang Helmberg were involved in the design of the study. Patrick Paul Torreiter, Camilla Drexler-Helmberg, and Petra Krakowitzky have conducted clinical visits. Patrick Paul Torreiter, Camilla Drexler-Helmberg, Peter Schlenke, Wolfgang Schimetta, and Wolfgang Helmberg wrote the draft version of the paper. Wolfgang Schimetta contributed statistical analysis and data visualization.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary files. Further inquiries can be directed to the corresponding author.

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