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Iron deficiency in blood donors: a review of the literature

Andreea Ionica

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NANTES UNIVERSITÉ

FACULTÉ DE MÉDECINE

Année : 2023

N°

THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

BIOLOGIE MÉDICALE

par

Andreea IONICA

Présentée et soutenue publiquement le 03 mars 2023

IRON DEFICIENCY IN BLOOD DONORS: A REVIEW OF THE LITERATURE

La carence martiale chez le donneur de sang : une revue de la littérature

Président : Madame le Professeur Marie Christine BENE

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Mr le Docteur Pierre-Antoine DEGUIGNE, Biologiste, EFS Angers

REMERCIEMENTS

Aux membres du jury

Madame le Professeur Marie Christine BÉNÉ

Vous me faites l'honneur de présider le Jury de thèse. Vous avez assumé également la direction de ma thèse. Je vous remercie pour toute la patience que vous m'avez accordée, pour le soutien et les encouragements que vous m'avez apportés pendant ce long temps de travail. Soyez assurée de ma sincère reconnaissance et de mon respect.

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Vous me faites l'honneur de juger cette thèse que vous avez codirigé également. Je vous remercie pour l'accompagnement dans le choix du sujet et de toutes les informations que vous m'avez transmis. Je vous remercie pour votre soutien et votre disponibilité. Soyez assuré de ma sincère reconnaissance et de mon respect.

Madame le Docteur Kalyane BACH

Vous me faites l'honneur d'accepter de juger cette thèse. Merci de votre disponibilité. Soyez assurée de ma sincère reconnaissance et de mon respect.

Madame le Docteur Myriam LEBRAS

Je vous remercie pour avoir accepté de juger cette thèse. Votre accompagnement lors de mes projets m'a été précieux. Soyez assuré de ma sincère reconnaissance, de mon respect et de ma gratitude.

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Monsieur le Docteur Pierre Antoine DEGUIGNE

Veillez accepter mes sincères remerciements pour avoir accepté de juger ce travail. Je vous remercie pour la somme de connaissances que vous m'avez transmises lors de ma formation. Soyez assuré de ma sincère reconnaissance et de mon respect.

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Vous m'avez accompagnée avec patience et précision dans les démarches administratives et dans mon parcours d'interne. Soyez assuré de ma sincère reconnaissance.

In memoriam

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Qui nous a quittés trop tôt et qui a marqué mon parcours d'interne en m'offrant l'accompagnement nécessaire pour arriver à ce point. Je vous serai toujours reconnaissante.

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J'ai la chance de vous avoir encore dans ma vie et d'apprendre de votre sagesse.

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Et

A tous ceux qui, à un moment donné, ont transformé ma vie avec leur présence. Merci à tous !

| Libellé (CNU) | Type d'emploi | NOM | prénom |
|--|----------------|--------------------|------------------|
| anatomie | MCUPH | SALAUD | Céline |
| | PUPH | HAMEL | Antoine |
| | | PLOTEAU | Stéphane |
| anatomie et cytologie pathologiques | ASM | LE LAN | Nowenn |
| | | LEPINE | Charles |
| | MCUPH | AUTAIN/RENAUDIN | Karine |
| | PUPH | TOQUET/ETIENNE | Claire |
| anesthésiologie - reanimation | | BOSSARD/BOISSEAU | Céline |
| | | MOSNIER | Jean-François |
| | ASM | DEMAY | Justine |
| | | FIEUZAL | Laure |
| | | SOUAB | Fouzia |
| | PUPH | ASEHNOUNE | Karim |
| | | LEJUS | Corinne |
| Anesthésiologie - reanimation | | ROQUILLY | Antoine |
| | | ROZEC | Bertrand |
| | PUPH | CINOTTI | Raphael |
| | ASM | BLANC | Alexiane |
| anglais | | LIEPPE | Chloé |
| | Contractuel 2D | BERNAY | Caroline |
| Bactériologie-virologie - hygiène hospitalière | PRCE | GAILLARD | Christine |
| | ASM | DRUMEL | Thomas |
| bactériologie-virologie ; hygiène hospitalière | ASM | RUFFIER D'EPENOUX | Louise |
| | MCUPH | BRESSOLLETTE/BODIN | Céline |
| | PUPH | CORVEC | Stéphane |
| | | LEPELLETIER | Didier |
| biochimie et biologie moléculaire | ASM | BLIN | Justine |
| | MCUPH | BACH/NGOHOU | Kalyane |
| | | GRATAS/RABBIA-RE | Catherine |
| | | HERBRETEAU | Guillaume |
| | PUPH | DENIS | Marc |
| | | MASSON | Damien |
| biologie cellulaire | MCF | GASCHET | Joëlle |
| | MCUPH | DAVID | Laurent |
| Biologie du développement et de la reproduction - gyneco. médicale | | LAMIRAUT | Guillaume |
| | PUPH | LEMARCHAND | Patricia |
| | PUPH | GOURRAUD | Pierre-Antoine |
| | ASM | CHAILLLOT | Maxime |
| | MCUPH | JEAN | Miguel |
| | | REIGNIER | Arnaud |
| biologie et biochimie moléculaire | | BARRIERE | Paul |
| | | FREOUR | Thomas |
| | MCF | MIGNE TRICHET | Valérie |
| | ASM | PINOT | Fanny |
| | MCUPH | BAILLY | Clément |
| | | ROUSSEAU | Caroline |
| | PUPH | BODERE/KRAEBER | Françoise |
| biostat. informatique med. et tech de communication | | BODET/MILIN | Caroline |
| | | CHEREL | Michel |
| | MCUPH | NGUYEN | Jean-Michel |
| | ATER | DUCHESNE | Léa |
| | ASM | HULO | Pauline |
| | | LUGAT | Alexandre |
| | | PERENNEC | Tanguy |
| | | PONS-TOSTIVINT | Elvire |
| | PUPH | BENNOUNA LOURIDI | Jaafar |
| | | CLASSE | Jean-Marc |
| | | SUPIOT | Stéphane |
| cardiologie | | VALMORI | Daniela |
| | ASM | LE RUZ | Robin |
| | | MARTEAU | Lara |
| | | MINOIS | Damien |
| | | PIRIOU | Pierre-Guillaume |
| | PUPH | BARUTEAU | Alban-Elouen |
| | | GOURRAUD | Jean-Baptiste |
| | GUERIN | Patrice | |
| | PROBST | Vincent | |

| Libellé (CNU) | Type d'emploi | NOM | prénom |
|--|---------------|---------------------|-----------------|
| cardiologie | PUPH | TROCHU | Jean-Noël |
| | ASM | DUBART | John-William |
| chirurgie digestive | | GERARD | Maxime |
| | | LALLEMAND | Louise |
| | | LESOURD | Romain |
| | PUPH | MIRALLIE | Eric |
| | PUPH | BLANCHARD LOUIS | Claire |
| | | MEURETTE | Guillaume |
| | ASM | GAUDET | David |
| | MCUPH | FARAJ | Sébastien |
| | PHU | DECANTE | Cyrille |
| | PUPH | LECLAIR | Marc-David |
| chirurgie maxillo-faciale et stomatologie | ASM | ANQUETIL | Marine |
| | | GUYONVARCH | Pierre |
| | | NHAM | Thanh-Thuy |
| | MCUPH | BERTIN | Hélios |
| chirurgie orthopedique et traumatologique | PUPH | CORRE | Pierre |
| | ASM | LAMBERT | François-Wavier |
| | | LATASTE | François |
| | | REGENNASS | Lucie |
| chirurgie plastique reconstructrice et esthetique | PUPH | NICH | Christophe |
| | ASM | LANCIEN | Ugo |
| | | VERDIER | Julien |
| | PUPH | DUTEILLE | Franck |
| chirurgie thoracique et cardio-vasculaire | | PERROT | Pierre |
| | ASM | DUBOST | Clément |
| | PUPH | BARON | Olivier |
| | | ROUSSEL | Jean-Christian |
| Chirurgie vasculaire - medecine vasculaire | ASM | LE CORVEC | Tom |
| | ASM | BENICHOU | Antoine |
| chirurgie vasculaire ; medecine vasculaire | PUPH | MAUREL | Blandine |
| | MCUPH | BAUD'HUIN | Marc |
| cytologie et histologie | | PILOQUET | Phillippe |
| | PUPH | HEYMANN | Dominique |
| dermatologie venerologie | ASM | ROBERT | Marine |
| | PUPH | BARBAROT | Sébastien |
| endocrinologie ; diabete et maladies metaboliques ; gyneco. medicale | | BOUSSEMART | Lise |
| | | QUEREUX | Gaëlle |
| | PUPH | DRENO | Brigitte |
| | ASM | SCHARBARG | Emeric |
| Epidemiologie, economie de la sante | PHU | SMATI-GRANGEON | Sarra |
| | PUPH | CARIOU | Bertrand |
| | | HADJADJ | Samy |
| | ASM | DUCHESNE | Léa |
| Gastro-enterologie - hepatologie - addictologie | MCUPH | HARDOUIN | Jean-Benoît |
| | | LECLERE | Brice |
| | PUPH | MORET | Leïla |
| | ASM | BOILEVE | Juliette |
| | ASM | GONDRAN | Hannah |
| | | MICHAUX | Quentin |
| | | MOISSET | Laure |
| | PAST | BOURREILLE | Arnaud |
| | PUPH | BRULEY des VARANNES | Stanislas |
| | | CORON | Emmanuel |
| genetique | | MATYSIAK BUDNIK | Tamara |
| | PUPH | TOUCHEFEU | Yann |
| | ASM | DEB | Wallid |
| | PUPH | BEZIEAU | Stéphane |
| Gynecologie-obstetrique - gynecologie medicale | | MERCIER | Sandra |
| | ASM | CARDAILLAC | Claire |
| | ASM | BURON | Charlotte |
| | | DEGEZ | Manon |
| Hematologie et transfusion | | RAGOT | Paul |
| | PUPH | WINER | Norbert |
| | PUPH | THUBERT | Thibaut |
| | ASM | ANTIER | Chloé |
| | BABUTY | Antoine | |

| Libellé (CNU) | Type d'emploi | NOM | prénom |
|--|--|-------------------|-----------------|
| Hematologie et transfusion | ASM | SORTAIS | Clara |
| | | VANTYGHM | Sophie |
| | MCUPH | HERMOUET | Sylvie |
| | PUPH | BENE | Marie-Christine |
| | | CHEVALLIER | Patrice |
| immunologie | | MOREAU | Philippe |
| | | TOUZEAU | Cyrille |
| | ASM | LEMOINE | Léa |
| | MCUPH | COLAS | Luc |
| | | MARTIN | Jérôme |
| maladies infectieuses ; maladies tropicales | PUPH | BLANCHO | Gilles |
| | | DANTAL | Jacques |
| | | JOSIEN | Régis |
| | ASM | ASQUIER KHATI | Antoine |
| | PUPH | BOUTOILLE | David |
| medecine d'urgence | | RAFFI | François |
| | ASM | NAVE | Suzanne |
| | | PINEAU | Gwénéolé |
| | MCUPH | JAVAUDIN | François |
| | PUPH | BATARD | Eric |
| Medecine d'urgence médecine général medecine generale | | LE CONTE | Philippe |
| | ASM | BELLIER | Amandine |
| | MCAMG | HILD | Sandrine |
| | ASM | CARLIER | Alexandre |
| | | COSTANZA | Sarah |
| | | GUEDON | Solène |
| | | MOREL | Thomas |
| | | NGUYEN-SOENEN | Jérôme |
| | | SCHMELTZ | Héloïse |
| | MCAMG | AMELINEAU | Jean-Baptiste |
| | | BRUTUS | Laurent |
| | | GRIMAULT | Charlotte |
| | | MAGNIN LARRAMENDY | Stéphanie |
| | | ROUSSEAU | Rosalie |
| | PAMG | BOUTON | Céline |
| | | HOMMEY | Nicolas |
| | | JEANMOUGIN | Pauline |
| | | JOURDAIN | Maud |
| | | VARTANIAN | Cyrille |
| | Medecine intensive - reanimation medecine intensive ; reanimation | PUMG | FOURNIER |
| | | RAT | Cédric |
| ASM | | RAYMOND | Matthieu |
| PUPH | | CANET | Emmanuel |
| | | REIGNIER | Jean |
| Medecine interne geriatrie et bio. du vieillissement - addictologie medecine interne geriatrie et bio. du vieillissement ; addictologie | ASM | RENAUD | Arthur |
| | ASM | CUBILLE | Marion |
| | | DELORME | Laetitia |
| | | ENFREIN | Antoine |
| | MCUPH | CHAPELET | Guillaume |
| | | ESPITIA | Olivier |
| | PUPH | AGARD | Christian |
| | | BERRUT | Gilles |
| | | de DECKER | Laure |
| | | HAMIDOU | Mohamed |
| | | POTTIER | Pierre |
| | PUPH | NEEL | Antoine |
| | ASM | DUCLOYER | Mathilde |
| | MCUPH | CLEMENT | Renaud |
| | ASM | LEPOITTEVIN | Laure |
| PUPH | PERROUIN/VERBE | Brigitte | |
| nephrologie | PUPH | GROSS | Raphaël |
| | ASM | LE CLECH | Alice |
| | | LEMAN | Claire |
| | | RONSIN | Charles |
| | MCUPH | FIGUERES | Lucile |
| neuro-chirurgie | PUPH | GIRAL | Magali |
| | ASM | SAMARUT | Edouard |

| Libellé (CNU) | Type d'emploi | NOM | prénom |
|--|---------------|------------------|-----------------|
| neuro-chirurgie | PUPH | BUFFENOIR-BILLET | Kévin |
| | ASM | COULOUME | Laura |
| neurologie | | LASSOZE | Simon |
| | | LEJEUNE | Flora |
| | PUPH | DAMIER | Philippe |
| | | DERKINDEREN | Pascal |
| | | LAPLAUD | David |
| | PUPH | JACOBI | David |
| | ASM | DUCLOYER | Jean-Baptiste |
| | | SERVANT | Marion |
| | MCUPH | LE MEUR | Guylène |
| | PUPH | LEBRANCHU | Pierre |
| nutrition | | WEBER | Michel |
| | MAST | PRUDHON | Emmanuelle |
| | ASM | GENDRE | Adrien |
| | | ROUAU | Gabriel |
| | PHU | MICHEL | Guillaume |
| | PUPH | BORDURE | Philippe |
| | | ESPITALIER | Florent |
| | | MALARD | Olivier |
| | | LAVERGNE | Rose-Anne |
| | | MORIO | Florent |
| ophtalmologie | ASM | BERNARD | Josselin |
| | | CAMUSET | Margaux |
| | | DAVID | Mélissa |
| | | JEGARD | Julien |
| | | MALOREY | David |
| | | SANTY | Coline |
| | | TORTIGUE | Marine |
| | PUPH | FLAMANT | Cyril |
| | | LAUNAY | Elise |
| | | LE GUEN/GRAS | Christèle |
| orthophonie | PUPH | BONNOT | Olivier |
| | ASM | LE CARPENTIER | Edouard |
| | MCUPH | GREGOIRE | Matthieu |
| | PHU | LAFORGUE | Edouard |
| | PUPH | DAILLY | Eric |
| | | JOLLIET | Pascale |
| | | VIGNEAU/VICTORRI | Caroline |
| | MCF | LANCELOT | Mathilde |
| | ASM | ASSIF | Myriam |
| | | GRIMAUULT | Dimitri |
| oto-rhino laryngologie | | HASSOUN | Dorian |
| | MCF | GUIHARD | Gilles |
| | | TOUMANIANTZ | Gilles |
| | MCUPH | CHAMBELLAN | Arnaud |
| | | FAYET | Guillemette |
| | PUPH | LE TOURNEAU | Thierry |
| | | PEREON | Yann |
| | ASM | GAUVRIT | Marie |
| | | MOUI | Antoine |
| | PUPH | BLANC | François-Xavier |
| parasitologie et mycologie | ASM | LAURIN | Andrew |
| | | SCHRECK | Benoit |
| | PUPH | BRONNEC/GRALL | Marie |
| | | SAUVAGET | Anne |
| | ASM | CHEVAL | Louis |
| | ASM | HERNANDEZ | Alexis |
| | | LE GAL | Antoine |
| | | PICHERIT | Alexandre |
| | | TROCHU | Theophane |
| | PUPH | BOURCIER | Romain |
| pediatrie | | DESAL | Hubert |
| | | SERFATY | Jean-Michel |
| | PUPH | FRAMPAS | Eric |
| | ASM | HERMAN | Julien |
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| Libellé (CNU) | Type d'emploi | NOM | prénom |
|--|---------------|------------|-------------|
| rhumatologie | ASM | LE PLUART | Adrien |
| | PUPH | LE GOFF | Benoît |
| sciences biologiques, fondamentales et cliniques sciences de gestion et du management sciences économiques sciences physico-chimiques et ingénierie appliquée à la santé thérapeutique et médecine de la douleur | | MAUGARS | Yves |
| | MCF | ORY | Benjamin |
| | MCF | ANGELE | Nathalie |
| | MCF | TESSIER | Philippe |
| | MCF | FOUCHER | Yohann |
| | PHU | LE BASTARD | Quentin |
| | PUPH | MONTASSIER | Emmanuel |
| | PUPH | NIZARD | Jean-Julien |
| | ASM | BOUTEILLE | Cécilia |
| | urologie | | BROUDEUR |
| PUPH | | BOUCHOT | Olivier |
| | | KARAM | Georges |
| | | RIGAUD | Jérôme |

LISTE DES ABREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome

BC: Before Christ

BMP: Bone Morphogenic Protein

Dcytb : Duodenal cytochrome B

DMT-1: divalent metal transporter protein

EFS: Établissement Français du Sang (French Blood Establishment)

EPO : Erythropoietin

ERFE : Erythroferrone

Hb : Hemoglobin

HJE: Hemojuvelin

HCP-1: Haem carrier protein 1

HIV: Human Immunodeficiency Virus

IMP: Integrin-Mobilferrin-Paraferritin

IRE: Iron Responsive Elements

IRP: Iron Responsive Proteins

mRNA: messenger Ribonucleic Acid

PCFT: Proton-coupled folate transporter

pH: Potential of hydrogen

RBC: Red Blood Cells

Tf : Transferrin

TfR : Transferrin Receptor

vCJD : variant Creutzfeld-Jacob Disease

WHO: World Health Organisation

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1. INTRODUCTION

Progress in immunology has allowed for the development of blood transfusion techniques and implicitly the evolution of blood donations (1,2).

The last WHO report published on their website in May 2022 provides one valuable piece of information: 118.5 million blood transfusions are performed worldwide each year (3). Blood donors are the key element in sustaining blood transfusion and the production of plasma-derived medicinal products. In high-income countries, almost 76% of the transfusions are administered to patients over 60 year-old whereas in low-income countries the target population is children under 5 year-old (54%) (3). Seventy-nine countries report collecting the blood supply from non-remunerated, voluntary blood donors while fifty-four countries are securing more than 50% of the blood supply from paid donors or through family and friends (3).

The total volume of blood in a human body is estimated at around 5000 mL (4). The maximal volume of blood that can be donated is 500 mL per donation, i.e. around 10% of the total volume. The quantity limitation is part of the mandatory criteria for giving blood. The common purpose of all the mandatory criteria is to obtain products of high quality without harming neither the donor nor the receiver (5).

Another mandatory criterion concerns the hemoglobin levels in donors. The minimum donor hemoglobin level to be accepted for blood donation is 13.5 g/dL for men and 12.5 g/dL for women, yet variations can be accepted to adjust the values according to a specific population. The check-up of hemoglobin levels is done according to pre-established protocols (5).

Verifying this specific parameter is important because hemoglobin is the main component of red blood cells (RBCs) and its role in gas exchanges and tissue oxygenation is essential (6). Depending on the level of decrease in hemoglobin concentration, such symptoms as fatigue, low physical and

cognitive performances and other manifestations derived from the lack of oxygenation can appear and have a negative impact on the donor's life (7–9).

As will be detailed later, iron is one of the main components of hemoglobin and thus it is necessary for the production of new RBCs (6,10,11).

Though its function is essential, the human body does not dispose of unlimited iron nor is able to take it in great quantity from the environment (9). The main stock is acquired at birth and in the first years of growth. Several mechanisms are meant to protect the body from the toxic effects of iron excess. One of the mechanisms is to bind iron and store it in specific cells (10,11).

Lately, a potential public health issue related to iron deficiency has been brought into discussion, more precisely the risk of iron deficiency among blood donors (12,13). One donation is equivalent to the loss of approximately 5 to 10% of the total body iron. In case of repeated donations, blood donors are subject to develop iron deficiency. As iron deficiency is asymptomatic, iron deficiency anemia can install over time, leading to an increased rate of deferral especially for frequent blood donors and create health issues for them (14).

This systematic review is meant to present a synthesis of recent publications that explored the frequency of iron deficiency in blood donors and the impact of iron supplementation after donation. The scope of this review is also to discuss the impact of iron deficiency among blood donors. Will this lead to a possible shortage in transfusion products in the future? Is it harmful to donors? If yes, how should donors be informed of the consequences brought by this benevolent act? How can the French Blood Establishment get involved in the medical care of donors? And more important, how to keep donors motivated to give blood when eligible again?

1.1 Background and rationale

1.1.1 The French blood supply

Since January 1st, 2000, the only public blood transfusion service in France, under the authority of the French Ministry of Health, is the EFS or *Établissement Français du Sang* (French Blood Establishment). The structure comprises 13 regional establishments proposing 126 collection sites and achieving 40.000 mobile collection sessions per year. About 1.6 million volunteer donors participate in blood collection and 1500 hospitals are supplied in blood-derived products for almost 1 million patients treated per year (15).

French blood donors do not receive any financial counterpart in exchange for their donation. They have access to a free snack immediately after donation to prevent hypoglycemia (15).

The EFS has the status of a governmental institution but enjoys a private regimen and is capable to ensure the national blood supply after achieving self-sufficiency. However, at present, after two years of pandemics associated with a lower flux of donors, self-sufficiency is becoming more difficult to achieve. The fact that, to ensure the protection of transfusion recipients, the criteria for selecting blood donors are getting stricter does not help either with collecting enough blood resources. The annual activity report of EFS 2021 showed that only 3.46% of the eligible French population donates blood at least once a year in the context of a rise in the number of needed transfusions (15).

The main selection criteria for blood donation in France are established based on WHO recommendations (5). Two special exemptions were allowed for France to better adapt the hemoglobin values to demographic variations. The first concerns the minimum level of hemoglobin to accept a blood donation. This exemption was accepted in order to apply the same values for the European and Overseas French territories, where due to populational characteristics, hemoglobin concentration is around 12 g/dL. The second exemption concerns collection of a blood sample by finger prick for prior testing, which is not applied systematically in France. However, a blood cell count is performed at

each donation. If the hemoglobin concentration is lower than 12 g/dL for women and 13 g/dL for men, the blood will not be used for transfusion purposes. Hemoglobin measurement after a finger prick will be applied to the donor during the next pre-donation clinic.

In the table below, the main donor selection criteria are presented. Exceptions may be applied concerning age (Canada, the United Kingdom or Scotland allow blood donation as early as the age of 17) or weight (donors weighing 45 to 50 kg are accepted in Singapore or India). Less blood will be collected from lighter donors, around 350 mL (5).

Table 1: WHO blood donation criteria summarized

| | |
|--------|--|
| Age | 18 - 65 years |
| Weight | minimum 50 kg |
| Health | <p>self-estimation of good health at the time of donation</p> <p>absence of any sign of infection</p> <p>six months after getting a tattoo</p> <p>12 months after getting a professional-made piercing and in the absence of any complications</p> <p>24h after a minor dental procedure</p> <p>one month after a major dental procedure</p> |
| Travel | <p>avoid donation after travelling to areas where mosquito-borne infections are endemic, e.g. malaria, dengue and Zika virus or if there is a history of travel or residence for defined cumulative exposure periods in specified countries or areas, in order to reduce the risk of transmitting variant Creutzfeldt - Jakob disease (vCJD) by blood transfusion.</p> |

In order to establish hemoglobin levels, a finger prick test can be performed prior to blood donation to evaluate the hemoglobin level. If the level of hemoglobin is inferior to the minimal accepted level, blood donation will not take place. Due to the questionable sensitivity (probability to correctly identify low hemoglobin) this test is not applied on a current basis but it is reserved for particular cases like a previous borderline level of hemoglobin (20).

1.1.2.3 Information of the donor

A large amount of information is available concerning the consequences of a blood transfusion. By contrast, the consequences of blood donation need further exploration.

By performing a simple search for “consequences of blood donation over the donor” with Google, the first answer is “*Does the donor suffer from any harmful effects after donating blood? Absolutely not*”. This return comes from the department of health of the Republic of Philippines. The second result states that “*Blood donation is safe*” published by the Mayo Clinic in July 2022. Other publications describe side-effects present for a brief period after donation. No awareness is published on the first page concerning iron loss and the risk of anemia after blood donation.

1.1.2.3 Physiological consequences of blood donations

Healthcare professionals working in blood donation establishments have long been questioning the impact of blood donation on the iron status of the donor and the risk of iatrogenic iron-deficiency anemia. The lifespan of RBCs is about 120 days and trillions are produced every day. Blood donation will involve an increase of the daily production of RBCs as a dynamic and highly efficient process. Several factors are however necessary for it to be efficient, notably iron availability (6,11).

Although iron is essential, the human body does not dispose of an unlimited amount of it, nor is able to take it in great quantity from the environment (9,10). The main iron stock is acquired at birth and in the first years of growth. Under normal circumstances, the small quantity of iron absorbed by the organism is mostly used to compensate for the losses through skin and epithelial desquamation in

the digestive tract. Most of the iron is recycled when RBCs are destroyed and deposited in specific organs and cells to be easy to use when needed. All these mechanisms are meant to protect the body from the toxic effects of iron excess. One of the mechanisms is to bind iron and store it in specific cells (11).

Lately, a potential public health issue related to iron deficiency has been brought into discussion, more precisely the risk of iron deficiency among blood donors (12,13). One donation is equivalent to the loss of approximately 250 mg of iron from a total of 3 to 5 g in the whole body and if this loss is not compensated, iron deficiency can progress towards anemia and lead to deferral of the concerned donors from future donations.

Iron is a transitional metal that can easily switch electrons with other elements. Due to its properties, iron's presence in hemoglobin is mandatory to assure the gas exchange function (10).

However, iron is not an element we can bring in great quantities to our body because excess iron stores can build in organs like the liver, heart, skin and other tissues (10,21). Repeated transfusions for example, can result in abnormal iron storing causing severe complications such as cirrhosis, liver failure, heart failure and even liver cancer (22).

On the other side, iron deficiency can lead to medical conditions. By donating one bag of blood, the approximate amount of lost iron is 0.25 g from a total of 3.5 to 5 g as presented previously. The reason the word lost is employed is because most of the iron contained in our body is recycled from senescent RBCs and reused to create new young ones. If iron stores are not replenished, erythropoiesis will be affected (9,10).

Normal absorption cannot replace the lost iron in a short amount of time; the process is submitted to the influence of various factors such as diet, habits, pregnancy or medical conditions (10,23).

1.2 Aims

1.2.1 The purpose behind this work

Several questions have driven this work, aimed at assessing how to best preserve the good health of blood donors while maintaining an adequate supply of blood for clinical purposes.

The first question was: is it important to check the iron status on a regular basis in new and frequent donors? If yes, which test has the highest sensitivity and is the easiest to perform?

The second question was: once the test is found and data extracted, how are the latter used to the benefit of donors?

The third question was: how to interact with donors at risk of developing anemia?

In order to answer these questions, a literature review was performed.

1.2.2 Organizing the study

This study is composed of three parts.

In the first part, information is presented on iron metabolism and iron deficiency anemia. This will be the basis of understanding the complexity behind iron regulation and the importance of regenerating lost iron resources to maintain a balanced erythropoiesis.

In the second part, donation protocols in France and in other European and non-European countries will be compared.

The third part is dedicated to discussing the results of published articles and to the evaluation of the effects of iron supplementation.

2. IRON. ELEMENTS OF PHYSIOLOGY AND PATHOLOGY

2.1 Iron metabolism

In nature, iron is one of the transition metals, known also under its symbol Fe. Its atomic number is 26, atomic mass 56 and it is mostly found at its oxidation states 3+ (ferric) or 2+ (ferrous) and rarely in its pure form. It has been known since 2000 BC and used through ages to produce weapons, jewels, and tools. The same metal, in the iron-porphyrin complex, is the core of hemoglobin, the protein contained by the erythrocytes that ensures the binding, exchange and transport of oxygen and carbon dioxide. Its role is due to iron's ability to function as an electron donor or acceptor, a property that is particularly useful for metabolic purposes (10).

2.1.1 Iron absorption

During the evolutionary process, selection has been made so that the organisms could retain iron stocks with minimum loss. Daily, 1 to 2 mg are lost through the digestive tract or skin desquamation. In women, another blood loss occurs during menstruation. The same quantity, in normal conditions, is absorbed from the diet. The main site where iron absorption takes place is the small intestine, more precisely the duodenum. Duodenal cells have complex mechanisms to uptake iron and to prepare its transfer towards storage structures. These mechanisms can be submitted to upregulation or downregulation, depending on the needs (10,23).

The essential protein sequence for making iron available for its target cells is formed by:

- Ferroportin: an efflux protein that transports iron from enterocytes and macrophages into the systemic circulation
- Transferrin: a highly affine iron carrier through the systemic circulation
- Transferrin receptors

- Ferritin: a protein that ensures physiological iron levels in the cell and a reversible iron storage at the same time.

It has been established through isotopic marking that the normal stock of iron is between 3 and 5 g, corresponding to 40-60 mg/kg. Approximately 70% of the iron is used by circulating RBCs and for daily erythropoiesis. Almost 10% is found in muscular myoglobin and 10% in cytochromes and enzymes. Up to 1g of iron is contained in hepatocytes in the form of ferritin. After the phagocytosis of senescent RBCs, the resulting iron binds to transferrin and is recycled via the macrophages at a rate of 25-30 mg/day. Even though transferrin-bound iron represents only 0.1% of total iron, the turnover can get up to ten times higher to sustain recycling mechanisms (24,25). These values are susceptible to variations depending on iron needs. For example, during their period of fertility, women require a higher intake of iron than men due to menstruation losses or during pregnancy when the transfer of iron from the mother to the fetus/child is active.

The only natural source of iron is diet.

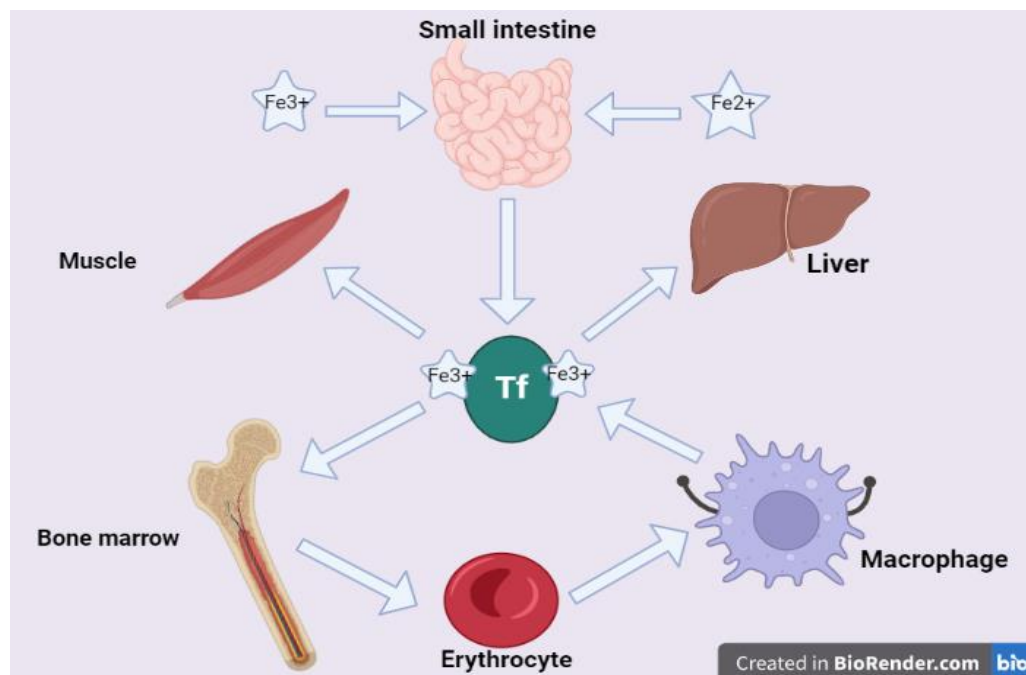


Figure 1. Transferrin iron bound distribution. Created with BioRender.com

Iron transfer to the systemic circulation passes through three main steps:

- Step one: transfer from the intestinal lumen to the intracellular compartment of enterocytes
- Step two: intra-cytosolic catabolism
- Step three: transfer from the intracellular compartment to the systemic circulation

Ferric iron or non-heme iron it is mainly found in plants and vegetables. Ferrous iron or heme iron is present in animal proteins and blood under the form of myoglobin or hemoglobin and represents the main source of iron (10).

As ferrous iron is ingested in its hemoglobin or myoglobin form, a first process of separation of the heme from the globin is necessary. Specific digestive enzymes ensure this step. Either the resulted iron-porphyrin complex or the heme is bonded and transported in the enterocyte by the heme-transporting proteins localized at the apical pole. Even though the mechanism of heme uptake is poorly understood, it is accepted that HCP-1 (heme carrier protein 1) is involved in the process. Lately, it has been proven that, combined with PCFT (proton-coupled folate transporter), HCP-1 is equally involved in folate absorption. While iron deficiency or overload has not been proven to have any influence on HCP-1 expression, it has been confirmed that hypoxia stimulates the production of HCP-1 mRNA (26). Hypotheses concerning the role of porphyrins or peptides resulting from globin digestion in favoring the contact between heme and HCP-1 are still being explored (27). Once the heme enters the enterocyte, heme-oxygenase enzymes separate the iron-porphyrin complex, freeing Fe^{2+} into the cytosol.

Ferrous and ferric iron have different properties due to their oxidation state. For example, ferrous iron is soluble at any pH while ferric iron is only soluble at a pH lower than 3.5, otherwise it precipitates in an insoluble form. Therefore, to be absorbed, ferric iron must be reduced to ferrous iron. Factors such as the low pH of gastric acid (between 1,5 and 3), ascorbic acid and ferrireductases such as Dcytb (duodenal cytochrome B reductase) engage in this process. Once the reduction reaction takes

place, ferrous iron is transported into the enterocyte by the transmembrane divalent metal transporter protein (DMT-1). One property of DMT-1 is that its expression is regulated by iron needs. In case of iron deficiency, the expression of the transporter increases and when the levels of iron are balanced or tend to exceed, the expression of the protein is considerably decreased (25).

Several mechanisms have been proposed concerning the path followed by ferric iron to be absorbed.

One of the hypotheses is that ferric iron enters the digestive system associated with non-heme proteins. In the acidic environment of the stomach, dissociation of the proteins takes place and Fe^{3+} is exposed. In the presence of ascorbic acid, provided by the diet or biliary secretions, ferric iron is either reduced to the ferrous form or enters in a ferric-ascorbate complex that will prevent it from precipitating when reaching the duodenum. Ferrous iron in the stomach needs to be chelated to avoid oxidation before reaching enterocytes. Chelation agents can be amino acids, sugars, or intestinal mucins (23).

Another theory has suggested a direct absorption of ferric iron via the IMP (integrin-mobilferrin-paraferitin) pathway, used by iron-mucin complexes to cross the apical pole of enterocytes (28).

Whether in a ferrous or ferric form, iron absorption is influenced by several factors.

Inhibition of absorption can occur when the diet is rich in phytates (plants), tannins or polyphenols (black tea, coffee, red wine), oxalic acid (spinach, nuts, white, black and red beans), calcium and animal proteins such as casein and even soy protein (29). Drugs such as proton-pump inhibitors used to treat hyperacidity in gastric ulcers are also known to inhibit iron absorption by making the pH more basic in the stomach (30).

On the other side, ascorbic acid is a strong promotor of iron absorption even in the presence of inhibitory factors, by chelating ferric iron and thus becoming a soluble form of iron in the basic pH of the duodenal secretion (29).

Iron absorption is also influenced by hypoxia but due to the complex mechanism of this process, it will not be discussed here.

The previously described mechanisms apply to other cells, and other trafficking pathways exist involving ferritin, haptoglobin or transferrin.

2.1.2 Iron in the cytosol

Once inside the enterocyte, ferrous iron accumulates into the cytosolic labile iron pool. From this pool, iron can be either transported to the site of use and storage or lost through desquamation of the intestinal epithelium.

When the demand is low and in order to maintain the intracellular equilibrium, the production of apoferritin is stimulated by the increased iron concentration effect on the iron responsive elements/iron responsive proteins system. Fe^{2+} will interact with apoferritin, which possesses a catalytic activity, and after oxidation, Fe^{3+} is stored under the form of ferritin (31). Enterocyte ferritin and the iron it carries will get lost via intestinal cell desquamation.

A part of iron from the labile iron pool is used for the biosynthesis of Fe/S clusters (25,32). Fe/S clusters are redox-active protein cofactors synthesized in mitochondria, the cytosol or nucleus. They have several roles: 1) electron transfer in mitochondrial respiratory complexes (aconitase), 2) reactive-oxygen species (ROS) production by complexes I, II and III, 3) cytosolic regulation of iron uptake through IRP1 (aconitase-like) 4) sensing oxygen in pulmonary arteries and carotids, 5) steroid synthesis in adrenal glands (ferredoxins)

If it is found in excess in the labile pool of iron and the ferritin is saturated, Fe^{2+} is used in the Fenton reaction. This is the process of decomposing hydrogen peroxide in hydroxyl radical in the presence of Fe^{2+} . Hydroxyl radical is a strongly ROS acting like a danger signal for the cell. Based on this property, the process of ferroptosis has been recently described as an iron-dependent cell death mechanism, different from any other mechanisms known until now (33).

In case of high demand, ferrous iron is rapidly exported through the basolateral membrane of the enterocyte in the systemic circulation by an efflux pump named ferroportin. Ferroportin is colocalized with hephaestin, a protein with an intrinsic ferroxidase activity that switches ferrous iron to its ferric form so that it can attach to the carrier protein transferrin, and enter the blood flow. Depending on needs, transferrin-bound Fe^{2+} is transferred to specific cells such as hepatocytes or medullar macrophages to be used or stored.

Iron transfer from transferrin (Tf) to the target cells is achieved through a membrane transferrin receptor (TfR). Two Tf receptors have been described: TfR1, which is expressed ubiquitously and regulated by iron levels, and TfR2, which is present on hepatocytes and erythroid precursors, and is regulated by ferritin concentrations (34).

Transferrin has a high affinity for iron and TfR1 has a high affinity for transferrin. This is why iron is delivered to the cell through receptor-mediated endocytosis. After the iron-Tf complex binds to TfR1 at the cell surface, a clathrin-coated vesicle generates an endosome also containing DMT-1 and a ferrireductase protein named Steap3 which surrounds the new complex. Through a proton pump, the content of the endosome becomes acid, causing the dissociation of iron from transferrin. The ferric iron released is rapidly reduced by Steap3 to its ferrous form and exported out of the endosome into the cytosol by DMT-1. The Tf-TfR complex is exported to the cellular surface where, under the neutral pH (7.4), Tf dissociates and becomes again available to capture more iron ions if body needs require it (34).

2.1.3 Regulation of iron absorption

Several mechanisms and molecules are known for their role in either blocking or enhancing iron absorption.

2.1.3.1 *Mucosal block*

This describes the capacity of an initial dose of iron to inhibit the absorption of a second dose administered two to three hours later.

This theory was first evoked in 1943 by Hahn after noticing that iron-deficient humans and dogs absorbed more radioactive ^{59}Fe than healthy subjects. According to his theory, when apoferritin (the iron-free form of ferritin) is saturated, no more iron can enter enterocytes. This involves that an iron-receptor mechanism allows to detect when cells are saturated with intrinsic iron and therefore prevents more iron from entering (35). The theory was perpetuated throughout the years without solid proof, as techniques for identifying the molecular mechanisms were not yet well understood. This theory has been forgotten since the discovery of hepcidin. However, newer research seems to revive the concept of a mucosal block associated with hypoxia-inducing factor (HIF) (36).

2.1.3.2 *IRE/IRA regulation*

The iron-responsive element (IRE)/iron regulatory protein (IRP) complex regulates the translation of such proteins as apoferritin, ferroportin or DMT-1 so that their expression can adapt to the iron flux or needs.

This mechanism involves the binding of iron responsive proteins IRP1 and IRP2 to iron responsive elements (IREs) in the untranslated regions of target mRNAs, thereby controlling mRNA translation or stability. Whereas IRP2 functions solely as an RNA-binding protein, IRP1 operates as either an RNA-binding protein or a cytosolic aconitase meaning that it can regulate the cellular metabolism.

To better illustrate the interaction between the IRE and the IRP, we can take as example the situation when iron is in deficit. In this case, iron retention will be regulated by the binding of IRPs in the IREs area of the 5' UTR zone of ferroportin and ferritin mRNAs, favoring the degradation of IREs and therefore blocking these mRNA translation into proteins. As a consequence, iron will neither be stocked nor exported in the extracellular compartment. In association, the binding of the IRPs on the IREs found in the 3' UTR zone of DMT1 and TfR1 mRNAs will stabilize the transcription of the corresponding mRNA and therefore favorize iron import (37).

Early experiments in cultured cells established the crucial role of IRPs in the regulation of cellular iron metabolism. More recently, studies in mouse models with global or localized IRP1 and/or IRP2 deficiencies uncovered new physiological functions of IRPs in the context of systemic iron homeostasis. IRP1 emerged as a key regulator of erythropoiesis and iron absorption by controlling the translation of hypoxia inducible factor 2 α (HIF2 α). IRP2 appears to dominate the control of iron uptake and heme biosynthesis in erythroid progenitor cells by regulating the expression of TfR1 and 5-aminolevulinic acid synthase 2 (ALAS2) mRNAs. Targeted disruption of either IRP1 or IRP2 in mice is associated with distinct phenotypic abnormalities. The combined disruption of both IRP1 and IRP2 is incompatible with life and leads to early embryonic lethality. Mice with intestinal- or liver-specific disruption of both IRPs are viable at birth but die later due to malabsorption or liver failure. Adult mice lacking both IRPs in the intestine exhibit a profound defect in dietary iron absorption due to the “mucosal block” caused by de-repression of ferritin mRNA translation (38).

2.1.3.3 *Hepcidin*

Hepcidin is a small peptide produced by the liver that regulates the production of ferroportin and implicitly, iron efflux into the systemic circulation.

In 2001, a novel peptide, isolated from human urine and synthesized by the liver during the acute phase of inflammation, was described. Named based on its synthesis site and activity, hepcidin is similar to a cysteine-based antimicrobial peptide found in insects and plants (39,40). In the course of exploring the mechanisms through which hepcidin interferes with bacterial and fungal metabolism, its key role in iron regulation was discovered (40,41).

A high intake of iron corresponds to a high efflux at the basal pole of enterocytes. Tissue iron overload seems to activate the BMP-HJE (bone morphogenic protein-hemojuvelin) complex and stimulate the phosphorylation of Smad proteins resulting in hepcidin synthesis (42). When in contact with ferroportin (the iron efflux pump), hepcidin reduces iron efflux through two mechanisms (43):

- binding to ferroportin to block iron transport.
- inducing, together with ubiquitin, a conformational change in the structure of ferroportin to facilitate its degradation

Consequently, ferroportin is internalized and degraded into the cytoplasm.

Factors that stimulate hepcidin release are transfusions, iron supplementation, genetic diseases or infectious/inflammatory diseases. Factors that inhibit hepcidin production are hypoxia, intense erythropoiesis, iron deficiency and sex hormones (41).

2.1.3.4 *Erythroferrone (ERFE)*

This hormone produced by erythroblasts as an inhibitory action on hepatic cells in order to decrease the production of hepcidin.

Among the impact of anemia on tissues, the most important is hypoxia, as a decreased level of hemoglobin cannot provide the proper amount of oxygen to the tissues. One of the most hypoxia-sensitive tissues is the kidney. Lack of oxygen will inhibit the hydroxylation and proteolysis of HIF and stimulate their migration to the nucleus where they activate replication of the erythropoietin (EPO)

gene. The EPO produced migrates through the blood flow to stimulate the production of erythroblasts. Large amounts of iron are thus required. To satisfy this increased need, the mechanisms that enhance iron absorption and rapid mobilization are activated. However, high iron uptake is strictly regulated by hepcidin, meaning that a system that can block the production of hepcidin must be used. These inhibitory stimuli have been recently discovered. One of the models that proved right was that in the context of hematopoietic stress associated with bone marrow destruction through irradiation or toxic substances administration, hepcidin production did not decrease in response to the induced anemia. The inhibitor involved at this stage is erythroferrone (ERFE), produced by erythroblasts upon EPO stimulation. After being released into the bloodstream, ERFE reaches hepatic capillaries and acts as an inhibitor of the BMP-Smad-HJE complex, which as described previously, is one of the main mechanisms triggering hepcidin synthesis (44–46).

2.1.3.5 *Ferritin*

Ferritin is the main form of reversible iron storage. It is ubiquitous in the cytosol of mostly hepatocytes and macrophages (31,47,48).

Depending on iron concentration and needs and under the influence of the IRE-IRP system, ferritin can either be exposed to lysosomal degradation in the context of iron deficiency in order to release the iron it contains or be excreted in the blood flow in CD63-rich extracellular vesicles (49).

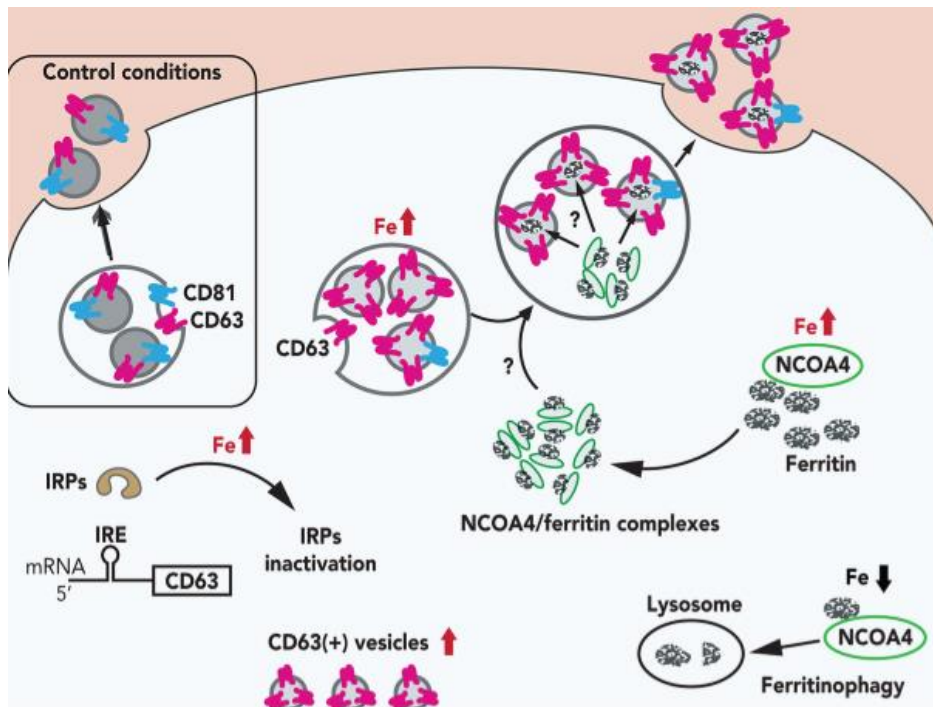


Figure 2. Ferritin metabolism (49)

Ferritin is formed by two individual subunits, ferritin H (heavy) with a ferroxidase activity, allowing the oxidation of Fe^{2+} and its incorporation as Fe^{3+} and ferritin L (light) which seems to constitute the surrounding structure of iron ions. One molecule of ferritin can accumulate up to 4500 iron ions. Its regulation is under the control of the IRE/IRP mechanism, and is influenced by intracellular iron concentration

In practice, assay of serum ferritin is used to estimate iron stores. Several studies have shown that circulating ferritin is not a recent product of the endoplasmic reticulum-Golgi pathway and signs of lysosomal transformation are present. Serum ferritin is mostly formed by L-ferritin and does not contain any iron ions (48).

2.2 Iron use in the bone marrow, erythrocytes and macrophages

2.2.1 Iron in the bone marrow and erythrocytes

Erythrocytes are anucleate cells produced by the hematopoietic bone marrow (50). Their precursors are erythroblasts, a cell line differentiated from the hematopoietic stem cell under the influence of cytokines and growth factors including EPO. At the medullary level, erythroblasts are organized into diffuse islets, organized around a macrophage. These macrophages have several roles in the formation of a competent erythrocyte: they stabilize erythroblasts in the islet using adhesion molecules, ensure cell proliferation and differentiation and capture the eliminated nucleus at the last stage of erythrocyte bone marrow maturation. Macrophages, by their ability to store intracytoplasmic ferritin, are an important source of iron, essential for the synthesis of hemoglobin. Under usual conditions, the body needs about 20 mg of iron daily for erythrocyte synthesis (50,51).

When the level of oxygen distributed to the tissues does not cover the needs, renal fibroblasts detect hypoxia and begin to produce and secrete EPO. Erythroid precursors of the bone marrow respond to EPO-induced signaling by an increase of erythroblast divisions and differentiation to mature erythrocytes. Another role of EPO is to stimulate erythroferrone production by bone marrow erythroblasts. The latter has the role of inhibiting hepcidin transcription in the liver by blocking signals transmitted by the BMP-Smad-HFE system (52).

2.2.2 Iron in macrophages

Intestinal absorption helps to maintain a balance between iron intake and losses. As absorption alone cannot cover the daily iron need, iron recycling and storing is necessary.

Macrophages play three main roles in the life span of RBCs (53,54). Firstly, they support the development and maturation of erythroid precursors in the bone marrow. Secondly, they maintain circulating RBCs by repairing and cleaning them from the damaged components produced by residual

mitochondrial activity. Thirdly, senescent RBC are cleared by macrophages in order to recycle iron from the heme component of hemoglobin.

In normal conditions, erythrocytes have a lifespan of about 120 days. While approaching the end of this lapse of time, the RBC's suffer structural and functional modifications which will be recognized by the macrophages from the liver and bone marrow, but mostly in the spleen. The reasons for which the spleen plays a key role in RBCs life cycle are not fully understood, but splenic anatomy helps to create starting points (55,56). The spleen structures are represented by the white pulp, specialized in adaptive immunity and the red pulp, separated by an intermediary marginal zone. The red pulp is mainly composed by a reticular web containing reticular cells and macrophages surrounded by numerous venous sinuses (56). Normal erythrocytes are freely circulating through these structures due to their elastic properties and their ability to deform. RBC's deformability depends mostly on the internal viscosity, the biodynamics of the membrane and cytoskeleton and alteration of the cell geometry (changes in size, shape or in the surface to volume proportions) (57).

Senescent or pathologic erythrocytes, due to structural and functional modifications, are less likely to get across the narrow capillaries which favors prolonged contact with macrophages (56,57).

The structural and functional modifications result in specific "cell death" signals stimulating the (54,55). The macrophages are equipped with various receptors to recognize senescent RBC modifications resulting from:

- the decreased activity of multiple enzymes;
- the gradual accumulation of oxidative damage;
- the accentuated loss of membrane in the form of microvesicles associated with an increased cell density;
- the redistribution of ions;
- the structural modifications of RBCs shape and deformability.

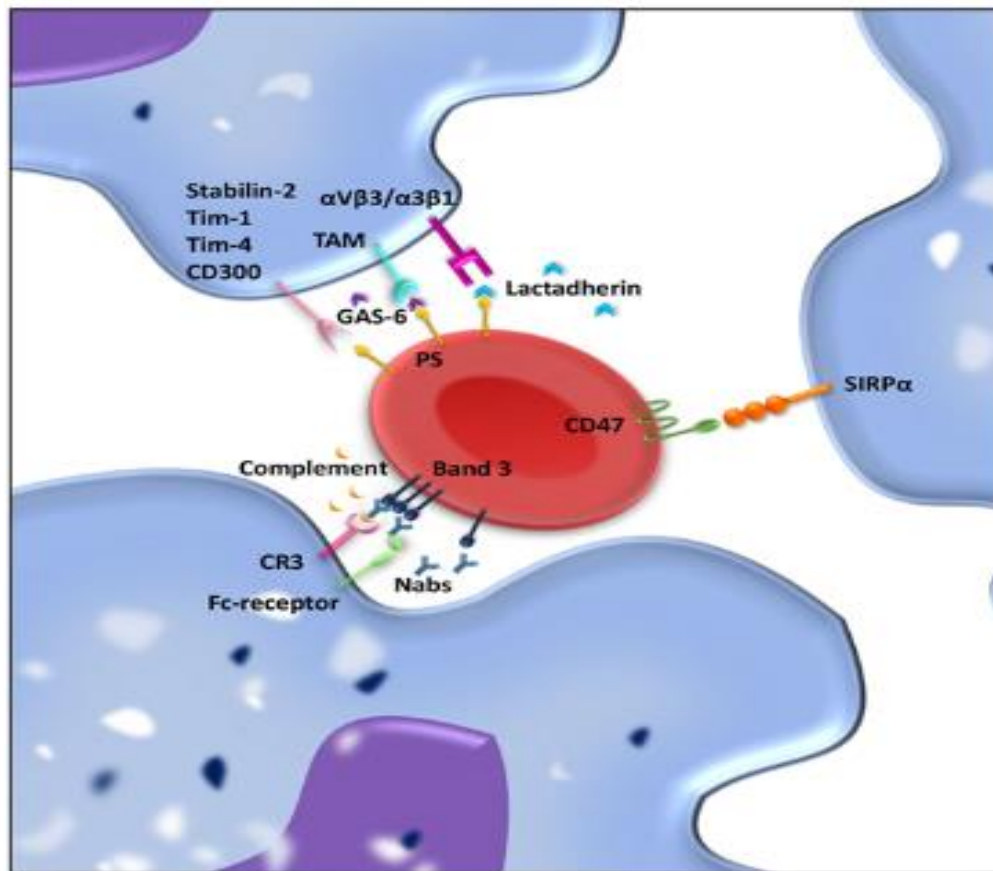


Figure 3. Mechanisms of erythrophagia stimulation (PS, GAS-6, lactadherin and band 3) and inhibition (CD47-SIRP alpha) (54)

RBCs destruction results from enzymatic catabolism within the macrophage phagolysosome. In this phagolysosome, hemoglobin is reduced to heme which, as previously discussed, contains in its center a ferrous atom that can act as a Fenton reactor and produce toxic oxygen radicals. Therefore, mechanisms controlling iron metabolism in the macrophage are essential for the cell's survival (58).

To be processed, heme from the phagolysosome needs to be transported into the macrophage's cytosol. This step is ensured by various transporters induced by a group of Heme Responsive Genes (HRG) (58–60). It has been recently described that HRG-1 specifically plays a key role in the activation of the transcription of important molecules such as HO-1 (heme oxygenase 1) and

ferroportin (60). Heme oxygenase 1 is a protein with enzymatic activity associated with the smooth endoplasmic reticulum which is involved in the degradation of the heme to biliverdin, monoxide carbon and iron (61). The presence of free iron ions will stimulate ferritin production by the macrophages and deposit iron when it is not rapidly exported (48,62).

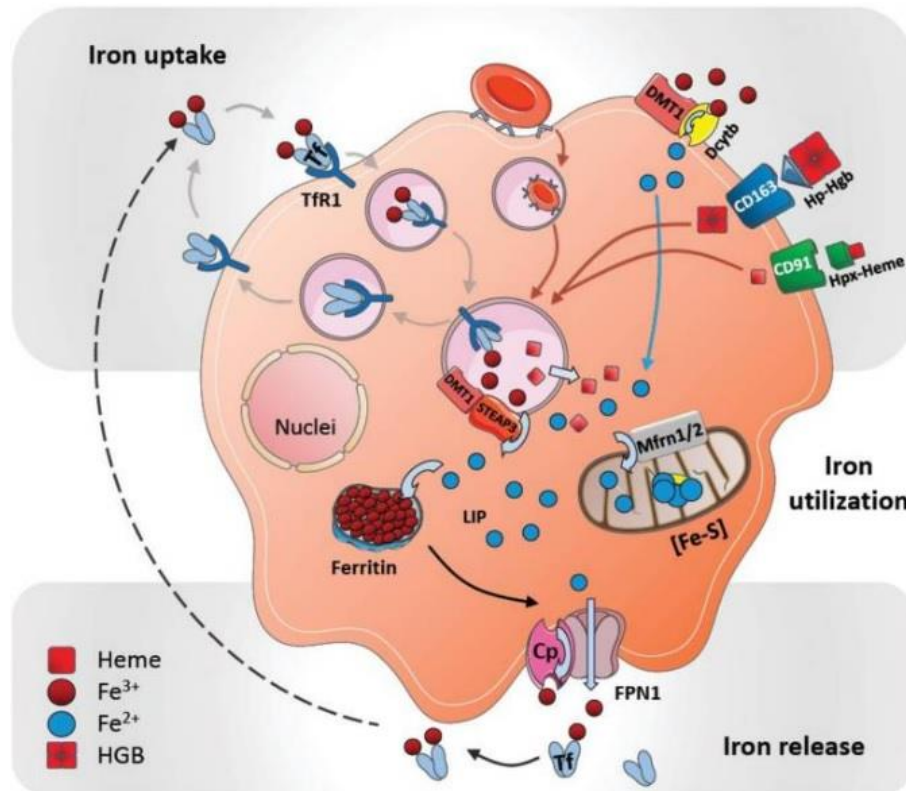


Figure 4. Iron metabolism in macrophages (53)

2.3 Anemia

2.3.1 Generalities

In ancient Greek, the word anemia or "*ἀναιμία*" has been used since the year 240 BC to describe a lack of blood. With scientific advances, anemia is now defined as a pathological condition that can derive from erythrocyte hypoproliferation, accelerated destruction of erythrocytes or acute or chronic bleeding (63).

Generally, anemias are classified according to their origin in central anemias and peripheral anemias.

2.3.1.1 *Central anemias.*

The causes of central erythrocyte hypo-proliferation are most often iron deficiency or lack of vitamin intake, especially vitamin B12 and folate. In other cases, this decrease in erythrocyte production is related to a pathology concerning the bone marrow. For example, in leukemia, bone marrow infiltration by blast cells blocked at an early stage of maturation impairs the development of other cell lines. Myelofibrosis or kidney diseases can also cause a decrease in erythropoietin production and in consequence a decrease in RBCs production (64).

2.3.1.2 *Peripheral anemias.*

Accelerated erythrocyte destruction occurs when RBCs have constitutional abnormalities. For example, in the case of sickle cell disease, defects in hemoglobin chains make it less affine for oxygen, less stable and leads to increased splenic destruction. Other causes of hemolysis are chronic and/or autoimmune diseases, viral or bacterial infections (especially infection with the *E. coli* O157:H7 strain), mechanical heart valves or post-transfusion formed antibodies against RBCs antigens (65–67).

Anemia that sets after blood loss can be acute (post-trauma hemorrhage or major surgery) or chronic (digestive bleeding, hemorrhoids, menses).

Chronic bleeding is blood loss that can go unnoticed for a long time and not be identified until a complication appears. For example, a chronic ulcer can perforate the gastric wall and result in an internal hemorrhage and a significant loss of blood. A digestive tract cancer can be the cause of active bleeding but because of the small quantity of lost blood, can go unnoticed until the appearance of clinical signs of anemia.

When donating blood, the maximum volume collected, as previously mentioned, is 500 mL. Even if this volume is not enough to constitute a significant loss, if the donor is already developing iron deficiency, it can accelerate the onset of anemia. For this reason, regular blood donations should be considered as chronic bleeding that could affect the health of the donor.

The discovery of anemia in a blood donor needs further investigations because other causes than iron deficiency can be responsible for a low hemoglobin level, as discussed previously.

2.3.2 Iron deficiency

Iron deficiency is essentially the result of a decrease of stores and is associated with a decrease in ferritin. This can occur either after acute or chronic loss of blood volume or through increased needs such as in adolescence or pregnancy (8).

It is only after the stocks are exhausted that serum iron levels drop and transferrin production increases. The ratio of these two elements (iron/transferrin) is represented by the transferrin saturation coefficient, used to assess the degree of iron transport capacity for cells that contribute to erythropoiesis. If the amount of iron is insufficient, hemoglobin production falters. Although the hemoglobin level is insufficient during all erythroblasts divisions, the mechanism of mitoses is not impacted. Since the signal that stops erythroblast divisions depends on the cytoplasmic level of hemoglobin, one or two additional mitoses are performed, leading to the formation of smaller RBCs. This results in hypochromic (hemoglobin concentration lower than 31%) and microcytic (erythrocyte size lower than $80 \mu\text{m}^3$) erythrocytes (63).

As a compensation mechanism, the number of transferrin membrane receptors increases to try and capture as much iron as possible (35).

Iron deficiency anemia is accompanied by more or less severe symptoms. These range from an overall decrease in energy and intellectual performance, a decrease in exercise tolerance through association with pica syndrome (ingestion of inedible and non-nutritive substances). The manifestations of iron deficiency in a person without other pathology can have a great impact on lifestyle (63,68).

2.3.3 Biological parameters of iron deficiency anemia (63)

In France, the first test used to establish a diagnosis of iron deficiency is a complete blood count. A decrease in hemoglobin concentration associated with microcytosis and hypochromia are the first indicators of iron deficiency anemia. These parameters are confirmed by a blood smear to examine the morphology of RBCs. The absence of reticulocytes is also a sign of poor regeneration.

Biochemical parameters such as serum/plasma ferritin levels, serum iron, transferrin levels, total iron binding capacity and transferrin saturation are also useful. Serum iron assessment has lost its interest since low serum iron can be induced by inflammatory anemia as well. It is now preferred to assess the ferritin level. Transferrin and transferrin-saturation are secondary elements of diagnosis.

A decrease in ferritin and transferrin saturation coefficient associated to an increase in transferrin, transferrin-binding capacity and soluble transferrin receptors is highly representative of iron deficiency.

Anemia occurs in the ultimate stage of iron deficiency. In practice, a correction of anemia is visible after the administration of iron supplementation.

2.4 Iron sources

2.4.1 Generalities

If left untreated, iron deficiency anemia can cause serious complications.

Faced with a biological assessment suggestive of iron deficiency anemia, it is necessary to first look for the primary causes. In most cases, the pathology can be highlighted but sometimes the origin remains unknown.

Since iron absorption increases when body needs increase, an iron-rich diet is the first step in iron supplementation.

The major dietary sources rich in iron are (69):

- Red meat: beef, pork or lamb and offal such as liver
- Poultry: chicken, turkey, and duck, and in particular their liver and red meat
- Fish/shellfish: oysters, mussels, sardines, anchovies
- Green vegetables of the cruciferous family: broccoli, kale, turnip greens, cabbage
- Beans: lima beans, pinto beans, peas, black-eyed peas
- Other iron-fortified foods: pasta, seeds, rice, or cereals

The absorption of iron at the intestinal level is stimulated by the concomitant administration of ascorbic acid (vitamin C) (70) . Examples of diet rich in vitamin C are (71):

- vegetables such as broccoli, spinach, tomato;
- fruits such as berries, kiwi, melon, grapefruit, citrus fruits (orange, lemon)

If diet does not provide the necessary quantity of iron, the administration of medicinal iron preparations is required.

The standard of care for iron deficiency anemia is oral administration of iron, but it can be associated with digestive disorders. Various ferrous salts are available on the market. Currently, no preparation has shown to be more effective than others. Parenteral administration is also possible, but it is reserved to particular cases and strict medical monitoring because side effects have also been described with parenteral administration (72).

Daily doses should be between 100 and 200 mg of elemental iron. It is advisable to administer iron tablets 2 to 3 hours before or after taking other treatments. Inhibition-type interactions have been described with calcium or magnesium as well as with antacids, leading to a decrease in iron absorption. On the other side, iron tablets can interact with the absorption of certain molecules such as methyldopa, penicillamine, cyclins, fluoroquinolones, or levothyroxine (68,69).

A first stage of accelerated increase in hemoglobin level of about 2g/dL can be noticed in the first 2 to 4 weeks after treatment initiation. This is associated with a decrease in symptomatology. Return to a normal hemoglobin value occurs on average after 8 weeks of treatment. Longer periods of supplementation (3 to 6 months) can be indicated if the etiology of an underlying pathology is not found.

Resolution of iron deficiency anemia might be delayed by poor compliance to the prescribed treatment as side effects can occur early after starting iron administration.

The most common side effects are digestive disorders: abdominal pain, constipation, nausea, and vomiting. Adjustments to the dose of treatment or of the administration schedule may contribute to better treatment tolerance. More severe but rare cases of esophagitis or digestive ulceration are described in the literature (73).

Other minor side effects are black teeth staining after intake of oral suspensions and dark feces.

It is important to perform a regular check-up of biological parameters to avoid iron overload. Signs of acute intoxication set in after a dose of 20 mg/kg. Clinical manifestations can range from severe digestive disorders to hepatic necrosis associating coagulation disorders, multi-organ insufficiency and coma. Oral iron preparations available in France are presented in Table 2.

Table 2 : Iron supplements available in France (source : eVidal) (74)

| Amount of iron per intake (mg) | Pharmaceutical form and quantity of iron salt per dosage unit | Trade name |
|--------------------------------|---|-------------|
| 32.5 | Ferrous succinate 100mg tablet | Inofer |
| 33 | Oral powder, 100 mg ferrous fumarate per gram | Fumafer |
| 33 | 245 mg capsule ferrous ascorbate | Ascofer |
| 34 | Syrup, 238 mg ferredetate per 5 MI | Ferrostrane |
| 50 | Drinkable solution, 400 mg of ferrous gluconate per vial | Tot'hema |
| 50 | Capsule of 173 mg ferrous sulfate | Timoferol |
| 66 | Tablet of 200 mg ferrous fumarate | Fumafer |
| 80 | Tablet of 256 mg ferrous fumarate | Tardyferon |

In case of intestinal malabsorption syndrome or bariatric surgery, severe iron deficiency, chronic bleeding or intolerance to oral therapy, intravenous iron administration may be necessary. This type of administration is performed under the supervision of a health professional, preferably in a hematology department.

The preparations available are as follows:

- fer dextran
- fer sucrose
- ferric gluconate

Intravenous iron administration is performed only after the patient has received a test dose in order to eliminate a potential risk of developing an allergic reaction. Severe side effects such as persistent pruritus or muscle and joint pain can be associated with this type of administration, but are less frequent.

Transfusion is a last resort solution in iron deficiency anemia, and is applied only in the presence of poor tolerance of anemia symptoms (chest pain, dyspnea at rest).

3. BLOOD DONATION AND DONOR MANAGEMENT

3.1 Blood donations in France

In France, blood donation is authorized between the ages of 18 and 70 and is regulated from a legislative point of view by the law of 4 January 1993, which protects anonymity, supports volunteering, imposes informed consent and reinforces the "non-profit" nature of the action. Only two centers are authorized to collect human blood and its components, the EFS and the Armed Forces Blood Transfusion Centre (CTSA). In 2020, more than five hundred thousand recipients benefited from a transfusion of blood or derivatives, resulting from 2,790,369 donations made by 1,618,632 donors (75).

Table 2, however, shows a downward trend in donations for the year 2020. A relevant justification is the occurrence of the COVID 19 pandemic associated with the lockdown period. There is some concern that this trend could be the indication of a trend that would question the self-sufficiency of blood and derivatives supply in France in the coming years.

Table 3: EFS annual reports (Dr. J. Y. PY., EFS Orleans)

| | Nb donations | Nb donors | Nb blood products | Nb recipients |
|-------------|---------------------|------------------|--------------------------|----------------------|
| 2015 | 2949317 | 1660363 | 3205370 | 529204 |
| 2016 | 2876062 | 1597458 | 3135906 | 520591 |
| 2017 | 2823769 | 1605997 | 3082178 | 522701 |
| 2018 | 2893137 | 1616499 | 3002160 | 519176 |
| 2019 | 2879003 | 1652771 | 3044777 | 530980 |
| 2020 | 2790369 | 1618632 | 2975396 | 522298 |

Data published in the activity report of EFS 2021 indicate an overall postponement rate of 9.6% versus 10.16% in 2020 and 14% between 2014 and 2017. This percentage is therefore decreasing with a constant average of 1.75 donations per person per year in accordance with the data of the last six years. Over the same period of 2015 to 2018 a decrease in the number of blood derivatives issued has been recorded. Conversely, statistics on the number of patients requiring blood transfusion show an upward trend (76).

3.2 Protection of blood donors

Compared to other countries of the European Union, the EFS benefits, as mentioned previously, from two derogations: a first concerning the systematic determination of hemoglobin and a second concerning the minimum level of hemoglobin authorized for blood donation. This avoids the creation of two different protocols for metropolitan France and for the DOM-TOM. The mandatory minimum hemoglobin threshold for blood donation is set at 12 g/dL for women and 13 g/dL for men. This derogation was accepted because, at the donation qualification laboratory, there is systematically a blood count and a blood smear in search of anemia. An interval of 8 weeks between two donations is currently required (77).

The search for pre-donation hemoglobin level on capillary puncture is not systematically performed but is mandatory for (77):

- a donor who comes for the first time,
- a donor who has not donated for two years,
- a donor for whom the last sample showed a hemoglobin value between 12 and 12.5 g/dL for women and between 13 and 13.5 g/dL for men.

During the clinical interview, the medical staff may also record the hemoglobin control on capillary puncture following a clinical history suggestive of anemia.

The hemoglobin level is an essential parameter because most of the transfusions are packed RBCs. If anemia is detected, the donor will be informed in writing and referred to the donor's attending physician for a more detailed evaluation. The RBC donation will not be used and will be destroyed or used for scientific purposes if authorized by the donor as mentioned previously (77).

The introduction of ferritin testing in the 1970s has led to numerous studies showing a decrease in iron reserves in regular blood donors (47). Currently, due to the ease of conducting its assay with high sensitivity, it represents the first choice in the balance sheet of evidence of iron deficiency in clinical practice (63). Indeed, a decrease in ferritin levels is not systematically correlated with a decrease in hemoglobin because anemia only sets in once iron reserves are depleted. Using the hemoglobin threshold as a criterion for selecting the concentrates sent (after eliminating all other contraindications) for transfusion yields an underestimation of the true frequency of iron deficiency in donors.

Further exploration is underway in France. A 1994 study (78) estimated a high prevalence of iron deficiency in the general population. A more recent study confirms the persistence of a trend towards anemia (79,80). It is therefore important to find ways to assess the frequency of post-donation iatrogenic anemias and the number of donors who should be dismissed to ensure that the self-sufficiency of blood product reserves can be preserved.

3.3 Donor protection measures abroad

The WHO proposes a general protocol for the selection of blood donors, based on Law 2004/33/EC of the European Union in order to standardize practices as much as possible with a view to global blood safety (81). Nevertheless, as populations are diverse, dissimilar needs have been identified and with them the need to provide an answer to a particular problem: how to manage iron deficiency?

Little information is available regarding the results that these changes may have brought to the protocols of different countries. The latest solid information is available in a study conducted in 2016 (82). Eight questions were sent to 28 European countries to gather information to evaluate donor selection algorithms, iron deficiency prevention and parameters assessed as part of a donor iron status assessment. Twenty-six countries have joined the study.

Table 4: Questions (82)

| | |
|-----------|---|
| 1. | Do you apply an invasive or non-invasive method for routine hemoglobin screening of donors? |
| 2. | What are the minimum hemoglobin levels for male and female donors to donate whole blood/platelets/plasma/red blood cells by apheresis? |
| 3. | What is the donor exclusion rate due to low hemoglobin? |
| 4. | What is the minimum interval between whole blood donations (separately for men and women if different) and what is the maximum number of donations that can be collected from male and female donors over a period of one year? |
| 5. | What is the acceptable range for the volume of whole blood donations? |
| 6. | Do you use a ferritin test (or other appropriate test - in this case, please specify) assess donors' iron stores? If yes, what algorithm do you use to detect/monitor iron deficiency (please briefly describe)? If it is not used routinely, are you aware of any research on donor iron stores in your country? |
| 7. | Please briefly describe how you manage iron-deficient donors (donation intervals, future donations, counselling, dietary advice, treatment) |
| 8. | If iron supplementation is administered, please specify whether the therapy is administered orally or intravenously/who covers the costs |

Data on hemoglobin assessment methods and donation intervals, frequencies and volumes are described in Tables 5 and 6.

Table 5: Methods for assessing hemoglobin (82)

| Country | Level of report | Method(s) used | | | |
|-----------------------|-----------------|-------------------|---|---|--|
| | | Non invasive | Invasive | | Bag sampling |
| Austria | National | Yes (minority) | Yes | Capillary blood Venous blood Grey area/questionable results | Yes (1 centre) |
| Belgium | National | No | Yes (all new donors and failure of Hb in a previous donation) | No | Yes (100%) |
| Bulgaria | National | No | Yes | No | No |
| Croatia | National | Yes (14% in 2014) | Yes (86% in 2014) | No | Yes (apheresis only) |
| Cyprus | National | No | Yes | Yes (apheresis only) | No |
| Czech Republic | Institutional | No | Yes | Yes (new World Bank donors) | Yes (regular leukocyte and apheresis donors) |
| Denmark | Regional | No | No | Yes (low Hb during a previous donation) | Yes |

| | | | | | |
|--------------------|---------------|----------------|---------------------------|--|--|
| Estonia | National | No | Yes | No | No |
| Finland | National | No | Yes | Yes (delayed due to low capillary Hb) | No |
| France | National | No | Yes (21%) | Yes (low capillary Hb) | Yes (100%) |
| Germany | Regional | No | Yes | No | No |
| Greece | National | Yes (1 centre) | Yes | No | Yes apheresis and some first-time donors |
| Italy | Local | No | Yes | Yes (low capillary Hb) | Yes (100%) |
| Latvia | National | No | Yes | No | No |
| Lithuania | Institutional | No | Yes | No | No |
| Luxembourg | National | No | Yes ("triggering events") | Yes (donor candidates and "triggering events") | Yes |
| Malta | National | No | Yes | Yes (weak Hb capillary and apheresis) | No |
| Netherlands | National | No | Yes | No (only special request) | No (for quality control purposes only) |
| Poland | National | Yes | Yes | Yes (once a year for regular donors) | No |

| | | | | | |
|-----------------------|---------------|-----------------------|--------------------------|---|---|
| Portugal | Local | No | Yes | Yes (apheresis donors) | Yes (bone marrow donors) |
| Romania | Institutional | No | Yes | Yes (apheresis donors or suspicious capillary Hb level) | No |
| Slovakia | National | No | Yes (mobile collections) | Yes (donations to BE) | Yes (donors tested only from capillary blood) |
| Slovenia | National | No | Yes 98% | Yes 2% (apheresis) | No |
| Sweden | National | No (under evaluation) | No | Yes (donor candidates) | Yes (registered donors) |
| Spain | Regional | No (from 2016) | Yes | Yes (weak capillary) | No |
| United Kingdom | National | No | Yes | Yes (weak capillary) | No |

Hb : hemoglobin

Table 6: Interval, frequency and volume of donations (82).

| Country | Level of report | Interval | | Donations/year | | Volume collected (mL) | |
|-----------------|-----------------|----------|----------|----------------|-----|-----------------------|---------|
| | | Women | Men | Women | Men | Units | Samples |
| Austria | National | 8 weeks | 8 weeks | - | - | 450±10% | 40 |
| Belgium | National | 2 months | 2 months | 4 | 4 | 470 max | 30 max |
| Bulgaria | National | 2 months | 2 months | 4 | 5 | 450±10% | 17 |
| Croatia | National | 4 months | 3 months | 3 | 4 | 450±10% | 35 |

| | | | | | | | |
|-----------------------|---------------|----------|----------|-------------------------------------|-----|--|---------|
| Cyprus | National | 120 days | 90 days | 3 | 4 | 450±10% | ≤10 |
| Czech Republic | Institutional | 10 weeks | 10 weeks | 4 | 5 | 450 target | 20 max |
| Denmark | Regional | 90 days | 90 days | 4 | 4 | 450±10% | ~ 40 |
| Estonia | National | 2 months | 2 months | 4 | 6 | 450±10% | ~ 35 |
| Finland | National | 91 days | 61 days | 4 | 6 | 465 target (415–515) | 30 |
| France | National | 8 weeks | 8 weeks | 4 | 6 | Max 500 (max 13% of the TBV*) | 30–40 |
| Germany | Regional | 56 days | 56 days | 4 | 6 | 500 target | 30 max |
| Greece | National | 2 months | 2 months | 3–4 | 4–6 | 450±20 | 20–30 |
| Italy | Local | 90 days | 90 days | 2 | 4 | 450 target | 40 max |
| Latvia | National | 9 weeks | 9 weeks | 4 | 6 | 450 | 35 |
| Lithuania | National | 2 months | 2 months | 4 | 6 | 405–495 | 20 |
| Luxembourg | National | 4 months | 3 months | 3 | 4 | 500±10% | 30 |
| Malta | National | 4 months | 3 months | 3 | 4 | 475±10% | 10–15 |
| Netherlands | National | 8 weeks | 8 weeks | 3 | 5 | 450–550 | 30 |
| Poland | National | 8 weeks | 8 weeks | 4 | 6 | 450±10% | ~ 18 |
| Slovakia | National | 4 months | 3 months | 3 | 4 | 450 target | 25 |
| Slovenia | National | 4 months | 3 months | 3 | 4 | 450±10% | 23 |
| Spain | Regional | 2 months | 2 months | 3 | 4 | 411–495 | 24 |
| Sweden | National | 12 weeks | 12 weeks | 3 | 4 | 450±10% | No data |
| United Kingdom | National | 12 weeks | 12 weeks | 7 times in 2 years (recommended) | | 475±10% | 20–35 |

*TBV = total blood volume

In 2016, ten participants reported that for specific categories of donors, ferritin testing is a priority. In Denmark, the Czech Republic and Italy, ferritin is more systematically measured. In Denmark (regional data), ferritin is measured in all primary donors, every ten donations and in case of previously low or high ferritin or hemoglobin. In the Czech Republic (institutional data), ferritin is

measured in all primary donors and in some cases in iterative donors. In Italy (local data), ferritin is measured once a year in regular donors, while in Cyprus different tests are carried out once a year (complete blood count, iron, ferritin) (82).

In seven countries (Austria, Croatia, France, Malta, the Netherlands, Portugal, and the United Kingdom), research on donor iron stores is still ongoing (82).

Responses regarding iron deficiency management were: referral of donors to a general practitioner/specialist, postponement of the donation and extension of the interval between donations, followed by donor counselling and dietary advice. Five participating countries reported performing assays to identify iron reserves.

When asked about supplementation techniques, responses from 14 of the 26 countries reported the use of iron supplements to varying degrees. The iron supply is administered orally and, in most cases, the costs are covered by blood transfusion services (82).

4. MATERIALS AND METHODS

The research was conducted between February 2022 and April 2022. The databases used were Google Scholar, PubMed and Cochrane databases with the key words “anemia”, “blood donors anemia”, ferritin in blood donors” “iron supplementation”.

The following inclusion criteria were applied:

- Studies published in English
- Publication year from 2010 on
- Assessing iron deficiency and evaluating iron deficiency anemia
- Specific population: blood donors
- Randomized trials.

Exclusion criteria were:

- Other causes of anemia in donors
- Explicit titles
- Meta-analyses and systematic reviews.

The study supervisor validated the reviews selection. One more article was added, that did not fulfill the time of publication criterion, for its scientific value (83).

Data were extracted manually by using specific criteria applied to all the articles and classified in an Excel Database.

A search was performed for outcomes concerning the prevalence of donor deferral for anemia, ferritin thresholds, methods of identifying hypoferritinemia and prevalence, deferral periods

recommended, evolution of ferritin levels in supplemented and non-supplemented donors, impact of administering an iron treatment on the deferral rate.

Results are reported following the recommendations given by PRISMA guidelines for systematic reviews (84,85).

5. RESULTS

5.1 Number of studies

After a thorough manual research (PubMed, Google Scholar), using the keywords indicated above, a total of 24 studies was selected.

5.2 Time and period of studies

As per inclusion criteria, these publications are recent (Annex 2), published after 2010. One exception is represented by a German study published in 1999 that was retained for its statistical value (83). Four studies (86–89) have been published in 2011, one (90) in 2014, two (91,92) in 2015, three (93–95) in 2016, two (96,97) in 2017, two (98,99) in 2018, two (100,101) in 2019, four (102–105) in 2020 and three (106–108) in 2021.

Nine studies have been performed in North America, including seven in the USA, one in Canada and the last one between Canada and the USA. Eleven studies come from Europe: three in the UK, one in Germany, three in the Netherlands, one in Switzerland, one in Denmark, one in Finland, one in Bosnia. One study issues from Iran, one from India and one from Australia. One study is a collaboration between Germany and the Austrian Red Cross.

The periods of data collection are not clearly presented in all publications.

5.3 Demographics

Donors are adults in 21 out of 24 studies, 16- to 18-year-old teenagers appear in two studies, and adolescents above 16 years of age in one study.

In all studies, male and female donors have been included in similar proportions.

5.4 Hemoglobinemia deferral threshold:

The minimum hemoglobin threshold for deferral is generally set at 125 g/L or 7.8 mmol/L for women and 135 g/L or 8.4 mmol/L for men. In some studies, a unique threshold of 12.5 g/dL has been chosen. This information is absent in 10 studies.

5.5 Anemia deferral prevalence:

Deferral due to low hemoglobin was reported in 10% of the total donors in a study conducted in the Netherlands (108). A longer deferral period due to low ferritin (12 months versus 3 months for low hemoglobin) is associated with a decrease of the low hemoglobin deferral frequency. The negative effect of prolonging the deferral period is a decrease in donor's availability to donate, mostly when ferritin level is equivalent to iron deficiency (<15 ng/mL).

5.6 Ferritin threshold:

The ferritin threshold to conclude about iron deficiency varies from 30 ng/mL to 15 ng/mL. Seven studies set the threshold for hypoferritinemia at 15 µg/L, three studies at 30 ng/mL, two studies at 26 ng/mL, one study at 25 ng/mL, one study at 10 ng/mL. Three studies propose different thresholds depending on gender: 30 ng/mL for women and 20 ng/mL for men (94,99,105). In four studies, no threshold is given although ferritin is measured (86,90,103,107).

A threshold of 20 ng/mL for male donors and 30 ng/mL for female donors has been chosen in two American study of teenage donors (16 to 18) (99,105). A 26 ng/mL threshold has been chosen in three American studies, without distinction between male and female donors (91,93,96). A threshold of 15 ng/mL has been chosen in six studies (83,89,97,101,104,108).

A 30 ng/mL threshold has been chosen in a Dutch prospective study to divide into two a cohort of 21 male donors followed during 8 weeks before and after blood donation (100). There was no difference between the low ferritin group and the normal ferritin group regarding the hemoglobin level prior to donation (Hb: 14.2 versus 14.8 g/dL). Two weeks after donation, a new ferritin assay was performed. Results showed a significant decrease of the ferritin levels in the low ferritin group. Unfortunately, the new hemoglobin values have not been reported.

A 25 ng/mL threshold has been chosen in a Canadian cohort study (98).

Hypoferritinemia screening

Hypoferritinemia is searched among all donors in the Netherlands, for each new donors and every fifth donation (108).

5.7 Hypoferritinemia prevalence

Hypoferritinemia (<15 ng/mL) is reported not to be more significantly prevalent between non-regular and regular donors in a study from Bosnia Herzegovina (106). The prevalence of hypoferritinemia is significantly higher when measured 45 days after the blood donation: 20% to 32.5 % for non-regular donors and 12.5 to 25 % for regular donors. This study was performed on a limited population of 80 donors.

In an Indian prospective study (104), ferritin decreases with the number of blood donations from 101.57 ng/mL (1 to 10 donations) to 56.69 ng/mL (more than 21 donations), with a prevalence of ferritin <15 ng/mL increasing from 3.7% to 27.6 % respectively.

In a Finnish prospective study (103), even though no ferritin threshold is given, the prevalence of hypoferritinemia is calculated after the definition of iron deficiency (ferritin <15 ng/mL). The results show a prevalence of 6 % among men, 20.6 % among premenopausal women, 10 % among post-menopausal women in a cohort of iron supplemented blood donors. In a multivariate analysis,

including dietary factors, the blood donation interval and the number of donations correlated significantly with hypoferritinemia as the main predictor of inter-individual variability, positively and negatively respectively.

5.8 Deferral

Models of deferral due to low ferritin have been proposed in the studies mentioned. Two studies are particularly interesting due to the large number of participants (99,108). Ferritin levels proposed for deferral start at 15ng/mL and go up to 20 or 30 ng/mL for deferral periods of 6 to 12 months.

Netherland is one of the few countries that established a deferral period varying from 6 months (ferritin between 15 and 30 ng/mL) to 12 months (ferritin below 15 ng/mL). Up to 6% of the total donation attempts are deferred due to low hemoglobin levels. Ferritin is assayed after blood collection in new donors and after each 5th donation. Iron deficient donors receive a letter with the deferral information. One interesting aspect is that by doing so, donated blood is not lost because the hemoglobin requirements are fulfilled (108).

5.9 Impact of deferral on blood donation

Two studies (98,108) found that deferral for low ferritin discouraged donors to return for new donations.

5.10 Ferritin value among donors

In a German study, ferritin values vary between 27.2 and 98.2 ng/mL, regardless of gender, and respectively between 34.7 and 145.3 ng/mL in men and between 19.7 and 57.6 ng/mL in women (83). In regular donors, values of 48.8 to 56.69 ng/mL were obtained after ferritin assay. Values of 98.2 to 101.57 ng/mL were observed in new donors (83).

A Swiss prospective study has compared the value of ferritin before and after several iterative donations: the baseline was measured at 43 ng/mL and decreased to 29 ng/mL after five donations (88). The measured ferritin values were comprised between 0.2 and 1019 ng/mL in the 160 612 analyzed samples.

Eight studies do not report the number or proportion of donors above established thresholds.

5.11 Effect of low ferritin on the return rate of donors

A Swiss study (88) evaluated the deferral rate and the return rate of donors before and after introducing the ferritin assay in routine in 2004. While the percentage of those deferred for low hemoglobin was higher before ferritin testing (2,8% from 1996 to 2003 versus 1,9% from 2004 to 2009), the return rate was lower : 72% and 75% at two and four years versus 60% and 64% after 2004.

5.12 Iron supplementation

Of the 24 studies, 16 address the issue of iron supplementation (Annex 3).

The hypoferritinemia thresholds for supplementation range from 10 ng/mL to 26 ng/mL.

The attitude towards blood donors is different. Depending on the study protocol, donors were included in four categories:

- Iron deficiency – iron supplementation
- Iron deficiency – placebo
- Iron deficiency – letter of information
- Iron deficiency – no information (control group)

Supplementation has been administered as follows: 100 mg of Fe⁺⁺ per day for 20 days or 37.5 mg per day for 24 weeks or 18 to 28 mg of elementary iron for 60 days (83,99,102).

The regular iron supplementation forms are either ferrous fumarate, iron gluconate, or elementary iron.

Treatment observance varies among the studies. In a multicentric clinical trial (96), Two groups of donors were prescribed iron supplementation at 38 mg or 19 mg, with compliance above 75% of the prescription in 76.6% and 82.0% respectively. The administration rate was between 75 and 100 % of the prescribed pills (44). The main reason for lower observance was forgotten (68% cases), followed by side effects (8 %), other medical reasons (5%), hard to swallow/dissolve in mouth (4%), refusal (4%), ran out of pills (3%) (96).

A multicentric randomized cohort study was conducted in the USA to compare iron supplementation (37.5 mg/day for 24 weeks) versus placebo (102). In this study, full recovery of total body iron required more than 100 days with iron supplementation and more than 24 weeks (duration of the study) without. The amplitude of this recovery is influenced by the ferritin level before donation: a lower ferritin level (<50 ng/mL) is associated with a higher increase in total body iron recovery, especially if the ferritin level is below 12 ng/mL.

5.13 Between-donation interval

Without blood supplementation, iron stores recovery relies only on iron absorbed from the diet. This aspect has been explored by an American study on teenage donors (105). Even after 12 months, donors were unable to replenish their iron stores. Beyond 12 months, 60 % female and 80 % male donors recovered from hypoferritinemia after only one previous whole blood donation.

In a British prospective cohort, the between-donation interval was significantly correlated with ferritin, but in this study, iron supplementation was not controlled (iron supplements prescribed or taken over-the-counter) (101). Hypoferritinemia (<15 ng/mL) was described among 21.19 % of the men for an inter-donation interval of 8 weeks versus 11.87 % of the men for an inter-donation interval

of 12 weeks. The same tendency was described in 25% of the women for a 10 weeks inter-donation interval versus 18.46 % for an inter-donation interval of 16 weeks.

5.14 Donation frequency

According to a Canadian cohort study, donation frequency, defined as the number of blood donations in a fixed time interval, is modified by measuring ferritin among blood donors (98). Indeed, donation frequency on a 2-year timespan was significantly lower after notification of hypoferritinemia (mean of 7.5 donations before and 4.5 donations after) and significantly higher after notification of normal ferritin (mean 4.4 and 4.5 after) for men. Women donors had comparable results, as the blood donation frequency for a two-year interval decreased from a mean 5.0 to 3.0 after announcement of low ferritin.

6. DISCUSSION

6.1 Synthesis

The causality between blood donation and iron deficiency has been repeatedly demonstrated in the studies presented. Regular donors are the most exposed group to iron deficiency post blood donation. The inter-donation interval depends on various factors and a standard period might not be appropriate for all donors. Ferritin is a more accurate reflection of iron deficiency tendencies in comparison with hemoglobin. Ferritin decreases significantly after the first 10 donations and its level stabilizes afterwards. Iron supplementation has proven its efficiency in re-establishing good iron reserves and reducing the number of deferrals for low hemoglobin. Still, it is not entirely clear how supplementation can be organized at a broader scale in order to be effective and accepted by the donors.

6.2 Iron supplementation strategies

Significant iron loss leads to anemia and other conditions such as pica, restless legs syndrome, preterm birth associated with low birth weight. Iron supplementation can compensate for this loss. Iron supplementation is not well tolerated in general and if prescribed to blood donors, risks are that they manifest a lower interest for blood donation. Furthermore, supplementation should be taken every day for several weeks in order to be effective. This might discourage donors from taking them and return once the iron levels normalize. There are two others main risks to take into consideration: 1) donors might take higher doses than prescribed and 2) iron supplementation could mask an underlying pathology.

The threshold used to define low ferritin determines the number of donors that may face deferral or iron supplementation. This value varies among studies, but the interval is from 30 ng/mL to 15 ng/mL. The lower the established value, the higher the probability of ignoring a future iron deficiency anemia.

Diet is not as effective as iron supplementation, but there should be recommendations even for donors without low ferritin or for donors who do not want to take iron supplements. The recommendation should cover all types of potential styles of diet (vegetarian, vegan, flexitarian ...).

While the 16 studies which explored iron deficiency in donors exposed significant improvement of iron stores in iron-deficient blood donors after the iron supplementation, expanding this practice to a higher scale comes with some challenges. Iron supplementation is delivered on the basis of a medical prescription and it comes after all other potential causes of iron deficiency anemia have been excluded. While the Blood Centers perform biological tests, clinical evaluation is limited. Therefore, under the current organization, doctors in Blood Centres cannot endow the risk of prescribing anemia treatment.

6.3 Blood donation interval

Reducing the frequency of blood donation is associated with higher levels of ferritin due to the greater time lapse available for the reconstitution of iron stores. Younger subjects may need more time to re-establish adequate stocks due to their higher requests. For example, women in childbearing age are more frequently exposed to developing iron deficiency due to menstrual loss and pregnancy.

Establishing a protocol based on hemoglobin concentration and ferritin levels to propose an adequate inter-donation interval might be helpful. Being healthy is the main criterion allowing a subject to give blood. This means that, other than iron deficiency, the donor should not have any pathological condition. Allowing to donate until a certain point where changes in hemoglobin cannot yet be seen but only a decreased ferritin, could be a solution. Using a higher threshold could prevent blood donation-induced iron deficiency anemia and supplementation. Deferral for a longer period of time could also be proposed to donors. In this way, they would preserve the feeling of gratification that accompanies the act of donating blood and consideration for their own health coming from the Blood Centres staff.

6.4 Ethics

In France, the action of blood donation is mentioned by the law by *Arrêté du 17 décembre 2019 fixant les critères de sélection des donneurs de sang*. It states that « *La poursuite des dons en aphérèse simple de globules rouges ne peut être effectuée que si la ferritinémie réalisée à l'occasion du premier don en aphérèse simple de globules rouges est supérieure à 20 ng/mL*» (the continuation of donations by simple red cell apheresis can only be carried out if the ferritin level measured at the time of the first donation by simple red cell apheresis is greater than 20 ng/mL). However, there is no stipulation that ferritin levels should be measured in whole blood donations.

Donors should receive an unbiased information before blood donation, in order to get informed consent.

6.5 Implementation in France.

FERRIDON (109) and UPRADON are the latest studies performed in France to identify the prevalence of iron deficiency in blood donors and to identify the subjects who present the greatest risk to develop iron deficiency.

6.6 Screening for iron deficiency

Ferritin is the gold standard to detect iron deficiency. This test is acceptable for blood donors, since a blood sample is already taken for other investigations during blood donation and performing the test is effortless. The costs should be taken into consideration though. Inflammation has to be excluded in the blood donors as ferritin levels are higher in this case.

7. CONCLUSIONS

Iron deficiency is a condition present among blood donors but in most of the cases it is not well correlated with hemoglobin levels. Iron deficiency anemia is the last phase of iron deficiency and is a cause of deferral.

Screening for iron deficiency by assessing the more sensitive ferritin assay helps identifying the subjects at risk of developing iron deficiency anemia.

Iron supplementation cannot be given to any patient without appropriate follow-up. It should be preceded by ferritin assay.

Blood donation is responsible for iron loss. Regular donors have a higher loss, proportional to the frequency of donation. This loss can be responsible for iron deficiency anemia, potentially symptomatic and can lead to the impossibility of continuing blood donations.

Iron supplementation could thus limit the prevalence of this iron deficiency anemia. The literature review presented here suggests that people at risk (women, regular blood donors) could benefit from screening when they donate blood, to prevent donation-induced anemia.

This screening could either be carried out at the time of blood donation for subjects identified at risk or even systematically (Figure 5). Screening could also be carried out individually, with information given to the donor (oral, poster at the blood donation center, leaflet delivery), under the authority of the general practitioner. General practitioners should also be formed to pay attention to this issue and to conduct regular anemia screenings in known regular donors or in those who express the intention of donating blood. This would improve iron deficiency anemia management by providing a follow-up of the biological parameters (measurement of hemoglobin and ferritin after iron supplementation).

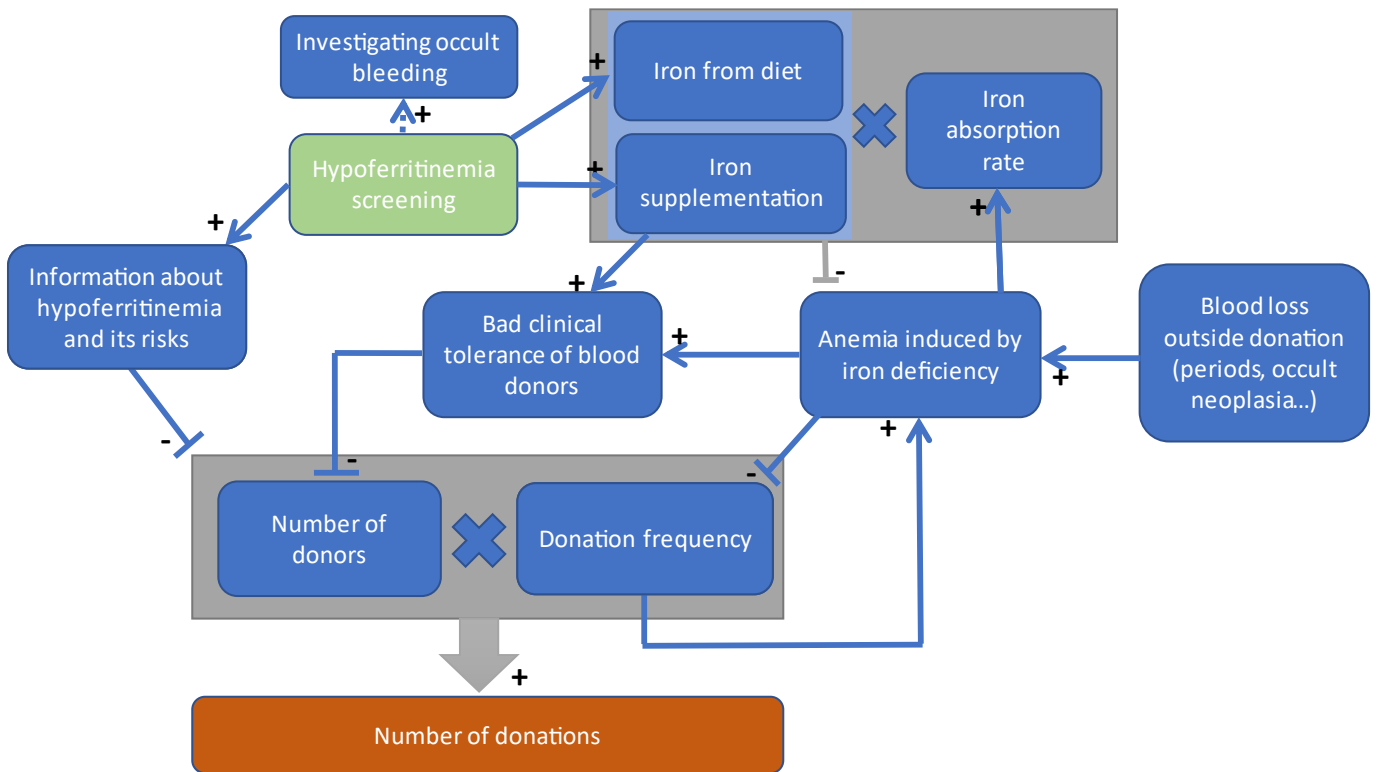


Figure 5: Cybernetic diagram of the consequences of hypoferritinemia screening on blood donation. Positive and negative relations are symbolized by (+) and (-) respectively

To date, there are no written recommendations to define the most appropriate treatment for the correction of iron deficiency. There are no contraindications apart from iron overload and allergy to excipients.

A meta-analysis should be performed including the studies analyzed in this review, taking into account the level of proof as the studies are very heterogeneous (multicentric prospective controlled double-blinded versus monocentric retrospective studies).

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NOM : IONICA

PRENOM : Andreea

Thesis title : IRON DEFICIENCY IN BLOOD DONORS: A REVIEW OF THE LITERATURE

ABSTRACT (10 lignes)

Donating blood exposes the donor to iron loss and can be responsible for iron-deficiency anemia. Iron homeostasis is strictly regulated and diet cannot always compensate losses. In 2021 in France no iron related assay was available to predict the prevalence of iron deficiency among blood donors. To this purpose, a review was carried out of the international peer-reviewed literature. It evidenced that the prevalence of hypoferritinemia increases with the frequency of donation and is associated with iron deficiency anemia in blood donors even before hemoglobin decreases. Different methods of iron supplementation have been tested and show an improvement on iron stores compared to placebo or no treatment. Screening for iron deficiency should be performed to protect donors and improve the long term sustainability of blood donations.

KEYWORDS

BLOOD DONATION – IRON DEFICIENCY – IRON SUPPLEMENTATION – REVIEW – IRON DEFICIENCY ANEMIA – SCREENING - FERRITIN

NOM : IONICA

PRENOM : Andreea

Titre de Thèse : LA CARENCE MARTIALE CHEZ LES DONNEURS DE SANG : UNE REVUE DE LA LITTERATURE

RÉSUMÉ

Le don de sang expose les donneurs à une perte régulière en fer qui peut être à l'origine d'une carence martiale. L'homéostasie des réserves en fer est soumise à des mécanismes stricts de régulation. En 2021, l'EFS ne disposait pas d'outil permettant de prédire la prévalence de la carence martiale chez les donneurs de sang. Dans ce travail, une revue de la littérature a été conduite à partir de publications internationales. Il en ressort que la prévalence de l'hypoferritinémie augmente avec la fréquence des dons et s'associe à une anémie ferriprive, avant même que le taux d'hémoglobine ne baisse. Plusieurs schémas de supplémentation en fer ont été testés avec un effet positif sur les réserves en fer par comparaison à un placebo ou à l'absence de traitement. Le dépistage de la carence martiale semble ainsi indiqué pour la protection des donneurs et pour conserver la pérennité des dons de sang sur le long terme.

MOTS-CLES

**DON DE SANG – CARENCE MARTIALE – SUPPLEMENTATION EN FER – REVUE – ANEMIE FERRIPRIVE -
DEPISTAGE - FERRITINE**

Annexe 1. Ferritin papers

| Référence. | 83 | 86 | 87 |
|---|---|--|---|
| Premier auteur | Alvarez-Ossorio L | Delaney M | Mozaheb Z |
| Date de publication | 2000 | 2011 | 2011 |
| Pays | Allemagne | Etats Unis | Iran |
| Période de l'étude | ND | décembre 2008 - mars 2009 | 2009-2010 |
| Age des donneurs (années) | 37+/-10 ans (moyenne +/-SD) donneurs réguliers ;31+/-11 ans chez les primo donneurs | âge moyen : 59,1 ans (H) ou 58,5 (F) | 24 à 65 ans (moyenne = 58,5 ans) |
| Seuil d'hypoferritinémie | < 15 ng/mL | NC | <20 ng/mL (carence martiale) et <15 ng/mL (érythropoïèse avec déficit en fer) |
| Valeurs observées | NC | hématocrite : 35.8% (H) ou 34.3% (F) | 42 ± 31 ng/mL |
| Seuil d'anémie (hémoglobinémie) | < 130 g/L (H) et <125 g/L (F) | NC | 125 g/L |
| Proportion de donneurs en dessous du seuil choisi | NC | 391 donneurs; seulement 104 ont été inclus dans l'étude suite à leur réponse dont 47 hommes et 57 femmes; 103 réponses ont été évaluées à la fin dont | 26 % et 15 % respectivement (deux dons par an) ; 58 % et 51% respectivement (trois dons en un an) |
| Donneurs récusés (nombre ou %) | NC | 391 donneurs en dessous du seuil d'hématocrite | 20 % des donneurs trois fois par an |
| Modification de la durée entre les dons | NC | NC | |
| Commentaires | étude rétrospective; évaluation ferritine pour les primo donneurs jusqu'à donneurs avec 50 dons; évaluation ferritine/Hb en fonction de la fréquence des dons /an | les donneurs qui ont répondu ont un niveau d'études supérieur et un suivi médical régulier; suite à un ajournement, le sentiment le plus exprimé est la déception; la majorité ont recherché des informations supplémentaires en ligne concernant l'hématocrite bas; la première attitude adoptée a été le changement de régime alimentaire puis la prise de suppléments de fer; quand ils sont informés qu'une visite chez le généraliste s'impose, 38% en moyenne vont le faire; la majorité de ceux qui ne vont pas le faire ne le considèrent pas nécessaire | Exclusion des donneurs avec supplémentation en fer |

| Référence | 88 | 89 | 90 |
|---|---|--|---|
| Premier auteur | O'Meara A | Pasricha SR | Moore C |
| Date de publication | 2011 | 2011 | 2014 |
| Pays | Suisse | Australie | Royaume-Uni |
| Période de l'étude | 1996-2009 | 2009-2010 | 2012-2013 |
| Age des donneurs (années) | 18 à 70 ans (moyenne = 47 ans) | Moyenne : 37,7 ans | plus de 18 ans |
| Seuil d'hypoferritinémie | <10 ng/mL | <15 ng/mL | |
| Valeurs observées | moyenne globale baseline = 43 ng/mL (0,2 à 1019) ; après 5 dons : moyenne = 29 ng/mL | moyenne globale = 27,2 ng/mL, donneurs refusés pour anémie : 8,4 ng/mL | |
| Seuil d'anémie (hémoglobininémie) | 133 g/L (H) et 123 g/L(F) | ND | |
| Proportion de donneurs en dessous du seuil choisi | 2,8 % avant 2004 (Hb), 1,9 % après 2004 (Hb) ; 6,7 % des hommes et 17,5 % des femmes (hypoferritinémie) | 22,60% | |
| Donneurs récusés (nombre ou %) | 2,8 % avant 2004 (Hb), 1,9 % après 2004 (Hb) | 10 % du total, avec 6,7 % pour cause d'anémie | |
| Modification de la durée entre les dons | Au choix du donneur si ferritinémie < 10 | ND | |
| Commentaires | Ferritinémie mesurée après 2004 seulement, dans une optique de dépistage et traitement d'une carence martiale | Biais d'attrition des patients non suivis. Biais de mesure : supplémentation par le médecin traitant ? | Article sur la mise en place d'un essai clinique sans résultats |

| Référence | 91 | 92 | 93 |
|---|--|---|--|
| Premier auteur | Bialkowski W | Magnussen K | Cable G |
| Date de publication | 2015 | 2015 | 2016 |
| Pays | USA | Danemark | Etats Unis et Canada |
| Période de l'étude | recrutement juin 2011 - avril 2012; étude des données: avril 2012 - mai 2014 | 2012-2014 | 24 semaines |
| Age des donneurs (années) | > 18 ans | ND | > 18 ans |
| Seuil d'hypoferritinémie | ferritine plasmatique <26 ng/mL ou ferritine sérique ≤30 ng/mL | <30 ng/mL | 26 ng/mL |
| Valeurs observées | 34.7 ± 34.9 ng/mL (H) et 19.7 ± 17.4 ng/mL (F) | Baseline : médiane = 63 ng/mL (H) et 34 ng/mL (F) | NC |
| Seuil d'anémie (hémoglobinémie) | 147 ± 12 g/L (H) ou 133 ± 10 g/L (F) | 135 g/L (H) et 125 g/L (F) | NC |
| Proportion de donneurs en dessous du seuil choisi | absence de réserves en fer: 17.2% (H) et 32.0% (F); érythropoïèse déficitaire en fer: 52.7% (H) et 74.6% (F) | 13 % (H), 43 % (F) | NC, remplacé par la mesure du fer total |
| Donneurs récusés (nombre ou %) | 62 (8,9%) | Baseline : 0,9 % (homme) et 3,9 % (femme) puis 0,3 % (homme) et 2,7 % (femme) | NC |
| Modification de la durée entre les dons | NC | | NC |
| Commentaires | absence de réserve en fer définie comme: ferritine <12ng/mL; érythropoïèse déficitaire en fer définie comme: $\log_{10} \text{TfR}/\text{ferritine} \geq 2.07$ | | critère de sélection: pas de don dans les 4 derniers mois; la ferritine sérique a été calculée en rajoutant 5% à la valeur de la ferritine plasmatique |

| Référence | 94 | 95 | 96 |
|---|--|---|--|
| Premier auteur | Gorlin J | Schotten N | Cable G |
| Date de publication | 2016 | 2016 | 2017 |
| Pays | Etats-Unis | Pays-Bas | Etats Unis |
| Période de l'étude | ND | 2013-2014 | 2 ans |
| Age des donneurs (années) | ND | ND | NA |
| Seuil d'hypoferritinémie | <20 ng/mL (F), <30 ng/mL (H) | 30 ng/mL | 26 ng/mL |
| Valeurs observées | baseline : 15,21 ng/mL (M) et 11,27 ng/mL (F) ; après supplémentation si hypoferritinémie : 28,81 ng/mL (M) et 21,98 ng/mL (F) | 98,2 ng/mL (nouveau donneur) vs 48,8 ng/mL (donneurs réguliers) | >à 26 ng/mL et < à 26 ng/mL |
| Seuil d'anémie (hémoglobinémie) | 125 g/L | ND | NA |
| Proportion de donneurs en dessous du seuil choisi | 85,9 % de donneurs en hypoferritinémie (H : 81,6 %, F : 87,8 %) | 8 % des nouveaux donneurs et 36 % des donneurs réguliers | NA |
| Donneurs récusés (nombre ou %) | 5,2 % de donneurs récusés pour hémoglobine basse en l'absence d'hypoferritinémie, contre 23,5 % en cas d'hyperferritinémie | ND | 5% avant étude, 3% après étude dans le groupe supplémente en fer, baisse significative |
| Modification de la durée entre les dons | NON | ND | baisse de la fréquence des dons dans le groupe non supplémente |
| Commentaires | | Ferritine non utilisée comme critère pour refuser un don dans cette étude | l'étude prend en compte uniquement les donneurs fréquents |

| Référence | 97 | 98 | 99 |
|--|--|--|--|
| Premier auteur | Di Angelantonio E | Goldman M | Vassallo R |
| Date de publication | 2017 | 2018 | 2018 |
| Pays | Royaume-Uni | Canada | Etats-Unis |
| Période de l'étude | 2012-2014 | 2016-2017 | 2017-2018 |
| Age des donneurs (années) | plus de 18 ans , moyenne = 45,3 ans (écart- type = 14,2) | ND | 16 à 18 ans (moyenne non précisée) |
| Seuil d'hypoferritinémie | <15 ng/mL | <25 ng/mL | 30 ng/mL (F) ou 20 ng/mL (H)/26 ng/mL (H+F) |
| Valeurs observées | baseline : 44,9 ng/mL (H), 24,6 ng/mL (F) ; 2 ans après don/12 semaines (H) et /16 semaines(F) : 36,3 ng/mL (H), 26,0 (F) ; 2 ans après don/8 semaines (H) et /12 semaines (F) : 25,7 ng/mL (H), 21,9 ng/mL (F) ; | baseline : 33,0 ng/mL (H), 22,2 ng/mL (F) , 2 ans après : 34,8 ng/mL (H) 25,2 ng/mL (F) | 26,9 %/31,9% |
| Seuil d'anémie (hémoglobinémie) | 135 g/L (H) et 125 g/L (F) | 125 g/L | 125 g/L (H) et 130 g/L(F) |
| Proportion de donneurs en dessous du seuil choisi | baseline hypoferritinémie : 8,6 % (H) et 24,8% (F) | Premier don : 2,6 % (H), 25,3% (F) ; Donneurs réguliers : 34,3 % (H), 51,0 % (F) | 26,90% |
| Donneurs récusés (nombre ou %) | baseline : 1,03 % (hommes) et 3,7 % (femmes) ; après 2 ans : 2,56 % des hommes pour anémie si don/12 semaines contre 5,72 % si don/ 8 semaines, 5,07 % des femmes pour anémie si don/16 semaines contre 7,92 % si don/ 12 semaines | | 21,8 à 38% (valeurs mensuelles, moyenne totale non disponible) |
| Modification de la durée entre les dons | OUI : essai randomisé ; intervalles testés : 8 , 10 et 12 semaines (hommes), 12, 14, 16 semaines (femme) | En cas d'hypoferritinémie, pas de convocation envoyée pendant 6 mois mais une lettre d'information préconisant une correction de la carence en fer. Pas d'interdiction formelle de don de sang | Dons suspendus 12 mois (H) ou 6 mois (F) |
| Commentaires | Valeurs intermédiaires pour des inter-dons de 10 semaines (hommes) et de 14 semaines (femmes) | Moins de retours pour don chez les femmes jeunes, primo-donneuses, avec hypoferritinémie dépistée avec information donnée de différer le prochain don ; 80 % des donneurs avec hypoferritinémie attendent 6 mois de plus (soit un an) avant reprise de don | Deux seuils différents évalués (critères BSI/NIH et critères REDS-II RISE) |

| Réf. | 100 | 101 | 102 |
|---|--|---|--|
| Premier auteur | Dijkstra A | Kaptoge S | Mast A |
| Date de publication | 2019 | 2019 | 2020 |
| Pays | Pays Bas | Royaume-Uni | Etats-Unis |
| Période de l'étude | 8 semaines ? (durée des dosages) | 2014-2016 | 2012-2013 |
| Age des donneurs (années) | âge moyen : 61,1 ans dans le groupe ferritine basse et 60,9 ans dans le groupe <i>ferritine normale</i> | plus de 18 ans | plus de 18 ans dont 21 % de plus de 60 ans |
| Seuil d'hypoferritinémie | cut-off: 30 ng/mL | <15 ng/mL | 12 -50 ng/mL et <12 ng/mL (hypoferritinémie modérée ou sévère) |
| Valeurs observées | ferritine moyenne: 19,1 ng/mL dans le groupe ferritine basse et 59.6 ng/mL dans le groupe ferritine normale | 4 ans après don/12 semaines(H) et /16 semaines (F) : 34,5 ng/mL (H), 28,2 (F) ; 4 ans après don/8 semaines (H) et/12 semaines (F) : 26,3 ng/mL (H), 22,6 ng/mL (F) ; | ND |
| Seuil d'anémie (hémoglobinémie) | pas de seuil d'anémie donné mais tous les donneurs étaient éligibles au don avec une Hb > ou =135 g/L malgré la ferritine basse trouvée chez certains | 135 g/L (H) et 125 g/L (F) | ND |
| Proportion de donneurs en dessous du seuil choisi | baisse significative de la ferritine dans le groupe normal (28.3 µg/L ± 12.3) dans les 8 semaines suivant le don. Avant don et 56 jours plus tard : 21.6 µg/L 10.9µg/L | 4 ans après don/12 semaines(H) et /16 semaines (F) : 11,87% (H), 18,46% (F) ; 4 ans après don/8 semaines (H) et/12 semaines (F) : 21,19 % (H), 25,00% (F) ; | 15,5 % avec ferritinémie <12 ng/mL, 60,1 % entre 12et 50 ng/mL |
| Donneurs récusés (nombre ou %) | NC | récusés pour hémoglobine basse : 4 ans après don/12 semaines (H) et /16 semaines(F) : 3,04 % (H), 4,42% (F) ; 4ans après don/8 semaines (H) et /12 semaines (F) : 5,94 % (H), 6,22% (F) ; | ND |
| Modification de la durée entre les dons | Les dons de sang total à répétition induisent un défaut d'érythropoïèse : baisse de l'hématocrite, des réticulocytes, du VGM si ferritine < 30 µg/L. intervalle de 56 jours entre deux dons. | OUI : essai randomisé ; intervalles testés : 8 , 10 et 12semaines (hommes), 12, 14, 16 semaines (femme) | ND |
| Commentaires | Ferritine et autres paramètres érythropoïétiques avant /post-don pendant 8 semaines; 21 donneurs réguliers en 2 groupes: 10 avec ferritine ≤30 ng/mL et 11 >; cut-off à partir d'une association avec l'HbA1c (dilution de l'hémoglobine glyquée lors d'une érythropoïèse efficace avec réduction d'environ 10% de la valeur vs pas de dilution si érythropoïèse inefficace) | Suite de l'étude 13, extension du suivi à 4 ans | |

| Référence. | 103 | 104 | 105 |
|--|---|--|--|
| Premier auteur | Lobier M | Reddy K.V | Vassallo R |
| Date de publication | 2020 | 2020 | 2020 |
| Pays | Finlande | Inde | Etats-Unis |
| Période de l'étude | 2015-2017 | 2015-2017 | 2017-2018 |
| Age des donneurs (années) | 45,3 (18 à 70 ans) | Moyenne : 33,5 ans (18 à 59 ans) | 16 à 18 ans (moyenne non précisée) |
| Seuil d'hypoferritinémie | ND | <15 ng/mL et [15;30] ng/mL | 30 ng/mL (F) ou 20 ng/mL (H) |
| Valeurs observées | 37,63 ng/mL | 101,57 ng/mL (1 à 10 dons), 73,97 (11 à 20 dons), 56,69(21 dons et plus), 23,57 (anémie) | 12.3 % (M) et 38.8% (F) |
| Seuil d'anémie (hémoglobinémie) | ND | 125 g/L | 125 g/L (H) et 130 g/L(F) |
| Proportion de donneurs en dessous du seuil choisi | ND | 8,4 % entre 15 et 30 ng/mL ; 7,8 % <15 ng/mL | 26,90% |
| Donneurs récusés (nombre ou %) | ND | 17 % (pour anémie) | 21,8 à 38% (valeurs mensuelles, moyenne totale non disponible) |
| Modification de la durée entre les dons | ND | NON | Dons suspendus 12 mois (H) ou 6 mois (F) |
| Commentaires | Le délai entre prélèvement et analyse augmenterait la valeur mesurée de la ferritinémie | | Deux seuils différents évalués (critères BSI/NIH et critères REDS-II RISE) |

| Référence | 106 | 107 | 108 |
|---|--|--|---|
| Premier auteur | Ćatović-Baralija E. | Clement M | Spekman M |
| Date de publication | 2021 | 2021 | 2021 |
| Pays | Bosnie Herzegovine | Pas clair, recherche faite en Allemagne sur des donneurs de la Croix Rouge Autrichienne ?! | Pays-Bas |
| Période de l'étude | 15 avril à 30 août 2019 | janvier 2010 à juin 2016 | 2017 |
| Age des donneurs (années) | 22-55 ans; 80 participants | ND | Moyenne : 52,1 ans (H), 42,4 (F) |
| Seuil d'hypoferritinémie | < 20 ng/mL = baisse des réserves; <15 ng/mL = cut- off déficit en fer | ND | <15 ng/mL et [15;30] ng/mL |
| Valeurs observées | 1a: Hb 155.55 ± 12,19; ferritine: 32.83. 1b:Hb 149.35 ± 13,47; ferritine: 23.36. 2a: Hb155.07 ± 12.04; ferritine: 43.10. 2b: Hb 149.03 ±13.76; ferritine: 26.63. 1a, 1b : donneurs réguliers avant don et 45 après (avant deuxième don);2a, 2b : 1a, 1b : primo donneurs ou donneurs irréguliers avant don et 45 après (avant deuxième don); différence significative d'Hb pré-post don et de la baisse de la ferritine pré-post don; pas de différence significative entre les deux groupes ni pour l'Hb ni pour la ferritine | analyse d'impact sur l'ajournement temporaire sur la future attitude des donneurs en fonction de leurs ressenti | <15 ng/mL (1,1 %) et 15 à 30ng/mL (1,6 %) |
| Seuil d'anémie (hémoglobinémie) | > 125 g/L (F); > 135 g/L (H) | ND | 8,4 mmol/L (H) et 7,8 mmol/L (F) |
| Proportion de donneurs en dessous du seuil choisi | seuil d'hémoglobine = critère d'inclusion; ferritine<20 ng/mL: 25% du groupe 1, 22,5% groupe 2 | ND | 2,70% |
| Donneurs récusés (nombre ou %) | NC | ND | 10,8 % (dont 2,7% pour hypoferritinémie) |
| Modification de la durée entre les dons | Non si Hb toujours dans le seuil accepté pour le don et surveillance ferritine. | don dans 19% des semaines pendant lesquelles les donneurs sont éligibles; l'ajournement pour un donneur récent est plus défavorable; si le nombre d'ajournements augmente, moins les donneurs réguliers reviennent | 6 mois de suspension si 15<ferritinémie<30 ng/mL ; 12 mois si ferritinémie<15 ng/mL |

| | | | |
|--|--|---|--|
| <p style="text-align: center;">Commentaires</p> | <p>intervalle minimal entre deux dons: 3 mois (H) à 4 mois (F); donateurs réguliers = 2 (F) ou 3(H) dons/12 mois; donateurs irréguliers: aucun don ou pas de don depuis 3 ans; classification dans 2 bras chacun avec 2 sous-groupes</p> | <p>grand échantillon: 123.000 donateurs. L'étude fait d'abord une synthèse bibliographique des articles qui évaluent de point de vue quantitatif et qualitatif l'impact de l'ajournement unique ou répété sur les habitudes à long terme des donateurs et après une évaluation théorique de l'attitude des donateurs basée sur les données disponibles dans l'échantillon donné.</p> <p>Focus sur les primo donateurs pour qu'ils subissent le moins d'ajournements possible</p> | |
|--|--|---|--|

| Référence. | 103 | 104 | 105 |
|---|---|--|--|
| Premier auteur | Lobier M | Reddy K.V | Vassallo R |
| Date de publication | 2020 | 2020 | 2020 |
| Pays | Finlande | Inde | Etats-Unis |
| Période de l'étude | 2015-2017 | 2015-2017 | 2017-2018 |
| Age des donneurs (années) | 45,3 (18 à 70 ans) | Moyenne : 33,5 ans (18 à 59 ans) | 16 à 18 ans (moyenne non précisée) |
| Seuil d'hypoferritinémie | ND | <15 ng/mL et [15;30] ng/mL | 30 ng/mL (F) ou 20 ng/mL (H) |
| Valeurs observées | 37,63 ng/mL | 101,57 ng/mL (1 à 10 dons), 73,97 (11 à 20 dons), 56,69 (21dons et plus), 23,57 (anémie) | 12.3 %(M) et 38.8% (F) |
| Seuil d'anémie (hémoglobinémie) | ND | 125 g/L | 125 g/L (H) et 130 g/L(F) |
| Proportion de donneurs en dessous du seuil choisi | ND | 8,4 % entre 15 et 30 ng/mL ; 7,8 % <15 ng/mL | 26,90% |
| Donneurs récusés (nombre ou %) | ND | 17 % (pour anémie) | 21,8 à 38% (valeurs mensuelles, moyenne totale non disponible) |
| Modification de la durée entre les dons | ND | NON | Dons suspendus 12 mois (H) ou 6 mois (F) |
| Commentaires | Le délai entre prélèvement et l'analyse augmenterait la valeur mesurée de la ferritinémie | | Deux seuils différents évalués (critères BSI/NIH et critères REDS-II RISE) |

| Référence | 106 | 107 | 108 |
|--|---|--|---|
| Premier auteur | Ćatović-Baralija E | Clement M | Spekman M |
| Date de publication | 2021 | 2021 | 2021 |
| Pays | Bosnie Herzégovine | Pas clair, recherche faite en Allemagne sur des donateurs de la Croix Rouge Autrichienne ?! | Pays-Bas |
| Période de l'étude | 15 avril à 30 août 2019 | janvier 2010 à juin 2016 | 2017 |
| Age des donateurs (années) | 22-55 ans; 80 participants | ND | Moyenne : 52,1 ans (H), 42,4 (F) |
| Seuil d'hypoferritinémie | < 20 ng/mL = baisse des réserves; <15 ng/mL = cut- off déficit en fer | ND | <15 ng/mL et [15;30] ng/mL |
| Valeurs observées | 1a: Hb 155.55 ± 12,19; ferritine: 32.83. 1b:Hb 149.35 ± 13,47; ferritine: 23.36. 2a: Hb155.07 ± 12.04; ferritine: 43.10. 2b: Hb 149.03 ±13.76; ferritine: 26.63. 1a, 1b : donateurs réguliers avant don et 45 jours après (avant deuxième don) 2a, 2b. Baisse significative d'Hb et de ferritine pré-post don; pas de différence significative entre les deux groupes ni pour l'Hb ni pour la ferritine | analyse d'impact sur l'ajournement temporaire sur la future attitude des donateurs en fonction de leurs ressentis | <15 ng/mL (1,1 %) et 15 à 30ng/mL (1,6 %) |
| Seuil d'anémie (hémoglobinémié) | > 125 g/L (F); > 135 g/L (H) | ND | 8,4 mmol/L (H) et 7,8 mmol/L (F) |
| Proportion de donateurs en dessous du seuil choisi | seuil d'hémoglobine = critère d'inclusion; ferritine<20 ng/mL: 25% du groupe 1, 22,5% groupe 2 | ND | 2,70% |
| Donneurs récusés (nombre ou %) | NC | ND | 10,8 % (dont 2,7% pour hypoferritinémie) |
| Modification de la durée entre les dons | Non si Hb toujours dans le seuil accepté pour le don et surveillance ferritine. | selon les données, les donateurs font un don seulement dans 19% des semaines pendant lesquelles ils sont éligibles; l'ajournement pour un donateur récent est plus défavorable que pour un donateur régulier. | 6 mois de suspension si 15<ferritinémie<30 ng/mL ; 12 mois si ferritinémie<15 ng/mL |
| Commentaires | intervalle minimal entre deux dons: 3 mois (H) à 4 mois (F); donateurs réguliers = 2 (F) ou 3(H) dons/12 mois; donateurs irréguliers: aucun don ou pas de don depuis 3 ans; classification dans 2 bras chacun avec 2 sous-groupes | grand échantillon: 123.000 donateurs. Bibliographie des articles évaluant l'impact de l'ajournement unique ou répété sur les habitudes à long terme des donateurs après une évaluation théorique de leur attitude basée sur les données de l'échantillon. Focus sur les primo donateurs pour qu'ils subissent le nombre d'ajournements le moindre possible | |

Annexe 2. Supplementation papers

| Référence | 83 | 88 |
|---------------------------------------|--|--|
| Premier auteur | Alvarez-Ossorio L | O'Meara A. |
| Date de publication | Octobre 1999 | Octobre 2011 |
| Pays | Allemagne | Suisse |
| Période de l'étude | ND | 1996-2009 |
| Age des donneurs (années) | 37+/-10 ans (moyenne +/-SD) donneurs réguliers ; 31+/-11 ans chez les primo donneurs | 18 à 70 ans (moyenne = 47 ans) |
| Seuil d'hypoferritinémie | < 15 ng/mL | <10 ng/mL |
| Proposition de supplémentation | seuil ferritine < 15ng/mL | Oui si ferritinémie<10 |
| Modalité de supplémentation | 567,7 mg sulfate ferreux voie orale (100 mg Fe élément) pendant 20 jours | Au choix : supplémentation en fer/changement alimentaire/espacer les dons |
| Compliance | méthode d'évaluation non mentionnée | ND |
| Effet de la supplémentation | amélioration rapide du taux d'Hb lors des dons suivants | Diminution globale du nombre de refus de don de sang pour anémie avant (2,8 %) et après (1,9 %) 2004 |
| Commentaire | indication d'un dosage de la ferritine en routine pour les primo-donneurs de sexe féminin pour détecter la carence en fer avant le don | Diminution plus marquée chez les femmes en âge de procréer (7,6 % à 4,8 %) |

| Référence | 91 | 92 |
|--------------------------------|---|--|
| Premier auteur | Bialkowski W | Magnussen K |
| Date de publication | Février 2015 | 2015 |
| Pays | USA | Danemark |
| Période de l'étude | recrutement juin 2011 - avril 2012; étude des données: avril 2012 - mai 2014 | 2012-2014 |
| Age des donneurs (années) | > 18 ans | ND |
| Seuil d'hypoferritinémie | ferritine plasmatique <26 ng/mL ou ferritine sérique ≤30 ng/mL | <30 ng/mL |
| Proposition de supplémentation | seuil ferritine < 26ng/mL | Fer per os |
| Modalité de supplémentation | 1er groupe: 60cp x 38 mg Fe; 2ème groupe: 60cp x 19mg Fe; 3ème groupe: 60cp x placebo | Envoi par la poste de comprimés de fumarate ferreux (330 mg) et acide ascorbique (60 mg), un tous les soirs avant le coucher |
| Compliance | 24 (ou 25) sur 692 donneurs ont abandonné l'étude pour cause d'effets indésirables du traitement ou pour des raisons médicales | ND |
| Effet de la supplémentation | Doses permettent la récupération des réserves en fer à un taux d'adsorption inchangeable de 4mg/jour; Ce n'est pas le fait de prendre du fer mais le fait de prendre des comprimés qui pose des problèmes lors d'une supplémentation car le nombre de perdus de vue est comparable entre le bras interventionnel et le bras placebo. Les effets indésirables touchant le système digestif semblent plus présents dans le bras interventionnel mais la différence est non significative statistiquement | Augmentation de l'hémoglobinémie globale et réduction de la fréquence des anémies |
| Commentaire | la supplémentation n'est pas à faire en systématique, sans être associée au dosage de la ferritine, car il existe le risque d'aggraver une éventuelle hémochromatose non identifiée | |

| Référence | 93 | 94 |
|--------------------------------|---|--|
| Premier auteur | Cable G | Gorlin J |
| Date de publication | 2016 | 2016 |
| Pays | Etats Unis et Canada | Etats-Unis |
| Période de l'étude | 24 semaines | ND |
| Age des donneurs (année) | > 18 ans | ND |
| Seuil d'hypoferritinémie | 26 ng/mL | <20 ng/mL (F), <30 ng/mL (H) |
| Proposition de supplémentation | oui, gluconate ferreux | Supplémentation en fer (envoyé par la poste) |
| Modalité de supplémentation | 215 donneurs, post don, 24 semaines, deux bras : 111 participants - 37,5 mg Fe (gluconate ferreux) vs 104 participants pas de supplémentation | Gluconate ferreux 325 mg (soit 38 mg de fer élémentaire/comprimé) |
| Compliance | 12 donneurs (9 du bras fer; 3 du bras sans traitement) se sont retirés avant la fin des toutes les visites médicales; 10 donneurs supplémentaires (6 du bras fer; 4 du bras sans traitement) avec des résultats d'hémoglobine manquants; 193 participants ont été analysés pour tous les paramètres (96 du bras fer; 97 du bras sans | 62 % : prise quotidienne ; 90 % : 5 jours par semaine |
| Effet de la supplémentation | 281 mg Fe total dans le bras supplémenté; -71,4mg de fer dans le bras non supplémenté; pas de récupération de la perte initiale sans supplémentation à la fin des 24 semaines. Plus le déficit est important au début, plus les réserves se refont vite après supplémentation; intervalle optimal de supplémentation : 0 et 4 semaines; bénéfice prouvé dans 88% respectivement 87% des donneurs supplémentés avec ferritine <26ng/mL et > à 26ng/mL. | Diminution du nombre de donneurs récusés. |
| Commentaire | donneurs avec ferritine < 26ng/mL et > 26ng/mL en proportion égale; dosage ferritine plasmatique et NFS avant le premier don, du J3 au J8 et à S2, 4, 8, 12, 16, et 24 post don; analyse des données: sur l'intervalle 0-16 semaines pour évaluer la durée optimale de la supplémentation et toutes les 8 semaines pour calculer la quantité totale de fer; variation inter-individuelle des pertes totales de fer, allant jusqu'à 100 mg | Effets secondaires (constipation, nausées, selles noires) à envisager. |

| Référence4 | 95 | 96 | 98 |
|--------------------------------|---|--|---|
| Premier auteur | Schotten N | Cable G | Goldman M |
| Date de publication | Octobre 2016 | 2017 | 2018 |
| Pays | Pays-Bas | Etats Unis | Canada |
| Période de l'étude | 2013-2014 | 2 ans | 2016-2017 |
| Age des donneurs (année) | ND | NA | ND |
| Seuils d'hypoferritinémie | 30 ng/mL | 26 ng/mL | <25 ng/mL |
| Proposition de supplémentation | Fer | oui, par suppléments /vitamines avec un contenu entre 17 et 38 mg de Fer élément | Oui en cas d'hypoferritinémie, par courrier, à mettre en place avec le médecin traitant |
| Modalité de supplémentation | ND | | ND |
| Compliance | NA | premier motif de non compliance: l'oubli (68%°) | ND |
| Effet de la supplémentation | NA | 58% des donneurs informés par une lettre de la carence ont pris la supplémentation, 5 fois plus que dans le groupe des ceux qui ont reçu la lettre mais sans consigne de supplémentation | Relativement moins de nouveaux dons à 2 ans (-40 %), mais en valeur absolue ce nombre devient similaire à la moyenne des donneurs qui ne présentaient pas d'hypoferritinémie initiale |
| Commentaire | Propose de supplémenter en fer les donneurs de sang ou de rallonger à 180 jours l'intervalle entre deux dons successifs | | Model de lettre informative ; 80% des donneurs qui ont reçu la lettre se sont abstenus de donner pendant 6 mois comme indiquée |

| Référence | 99 | 101 | 102 |
|--------------------------------|---|--|--|
| Premier auteur | Vassallo R | Kaptoge S | Mast A |
| Date de publication | Décembre 2018 | 2019 | 2020 |
| Pays | Etats-Unis | Royaume-Uni | Etats-Unis |
| Période de l'étude | 2017-2018 | 2014-2016 | 2012-2013 |
| Age des donneurs (années) | 16 à 18 ans (moyenne non précisée) | plus de 18 ans | plus de 18 ans dont 21 % de plus de 60 ans |
| Seuil d'hypoferritinémie | 30 ng/mL (F) ou 20 ng/mL (H)/26 ng/mL (H+F) | <15 ng/mL | 12 -50 ng/mL et <12 ng/mL (hypoferritinémie modérée ou sévère) |
| Proposition de supplémentation | Fer élémentaire | Supplémentation en fer possible en dehors du cadre de l'étude (médecin traitant) | Supplémentation en fer |
| Modalité de supplémentation | 18 à 28 mg per os 60 jours | ND | 37.5 mg Fe élémental sous forme de gluconate de fer par jour pendant 24 semaines vs placebo à partir de la première évaluation post -don (3 à 8 jours post-don) |
| Compliance | ND | ND | 92,5% sur 195 donneurs à la fin (215 donneurs initialement) |
| Effet de la supplémentation | ND | Augmentation de la concentration d'hémoglobine parmi les donneurs qui ont été supplémentés | Récupération des réserves totales en fer |
| Commentaire | Mesures dans la seconde étude | | |

| Référence | 104 | 105 | 108 |
|--------------------------------|---|---|---|
| Premier auteur | Reddy KV | Vassallo R | Spekman M |
| Date de publication | 2020 | 2020 | 2021 |
| Pays | Inde | Etats-Unis | Pays-Bas |
| Période de l'étude | 2015-2017 | 2017-2018 | 2017 |
| Age des donneurs (années) | Moyenne : 33,5 ans (18 à 59 ans) | 16 à 18 ans (moyenne non précisée) | Moyenne : 52,1 ans (H), 42,4 (F) |
| Seuil d'hypoferritinémie | <15 ng/mL et [15;30] ng/mL | 30 ng/mL (F) ou 20 ng/mL (H) | <15 ng/mL et [15;30] ng/mL |
| Proposition de supplémentation | Supplémentation en fer | Fer élémentaire | Non systématique, si carence martiale symptomatique |
| Modalité de supplémentation | NA | 18 à 28 mg per os 60 jours | NA |
| Compliance | NA | ND | NA |
| Effet de la supplémentation | NA | NA | NA |
| Commentaire | Propose de supplémenter en fer les donneurs de sang avec une ferritinémie basse ; CRP non dosée | Pas de comparaison entre patients supplémentés/non supplémentés, cohorte observationnelle | Dose non exprimée |