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Review

Optimisation of Blood Donor Nutrition: Blood Donor Health Improvement Studies

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Key Words
Blood donation • Diet for blood donors • Nutrient effects on blood donors • Iron deficiency

Abstract
This review provides an analysis of the current literature on the health and nutrition of blood donors, examining key aspects that affect the quality of donated blood and the well-being of donors. The review discusses effective iron absorption facilitated by key nutrients and presents evidence on the importance of a balanced diet rich in essential nutrients, such as vitamin B_{12} and folic acid. The review examines the differences in iron levels between men and women and highlights the role of sex hormones in regulating iron metabolism. In addition, the review discusses the link between psycho-emotional well-being and diet, showing that proper dietary habits can improve mental health, reduce stress, and enhance the donation experience. This article provides practical recommendations to support donor well-being and the effectiveness of blood donation programmes worldwide. By highlighting the differences between a modern diet and a diet tailored specifically for blood donors, we aim to emphasise the importance of a nutrient-dense diet for blood donors, which is critical for effective recovery and overall health maintenance. It is important to understand and incorporate different nutrient-dense foods that influence iron absorption for optimal health in blood donors. Donor health is also influenced by regular physical activity and psycho-emotional well-being. The 'healthy donor effect' and its implications for maintaining higher standards of donor health are explored in this review. This article highlights the fact that the diet of blood donors is influenced by gender, as men and women have different nutritional needs and physiological responses, particularly with regard to iron levels and recovery. The importance of enhancing or inhibiting iron absorption provides valuable evidence for food fortification as a cost-effective solution to reduce iron deficiency in blood donors.

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Introduction

Blood donations play a vital role in medical treatment and emergency care, providing essential components for surgery, trauma care, cancer treatment, and chronic diseases [1]. Blood donors are an essential part of the healthcare system. The blood component quality requires adherence to the specified properties and characteristics of the blood component delivered to the consumer. Strict adherence to approved standards and procedures is required at all technological stages and provides a guarantee of the quality of blood components and their finished products [2], from the planning of the donation to the receipt of the finished products and their storage conditions. An adequate blood supply is crucial for the treatment of many diseases, such as anaemia or cancer [3].

Nutrition plays a critical role in the health and performance of blood donors [4]. Proper nutrition before and after blood donation has a direct impact on blood quality, donor well-being, and speed of recovery. Several key aspects highlight the importance of nutrition for blood donors: blood quality, prevention of weakness and dizziness, faster recovery after blood donation, long-term health of donors, and strengthening of the immune system [5].

The declining pool of potential donors has a negative impact on the volume of blood donated in many countries [6]. It is well known that the decline in the donor pool against the background of the growing demand for blood components and preparations is a pressing issue in modern transfusion medicine, as the number of donors is decreasing, especially in the aftermath of the SARS-CoV-2 pandemic. In Mexico, for example, the number of donors decreased by 22% between April and May 2020, compared to the same months in 2019 [7]. Some studies have identified the following main causes of the decline in the number of blood donors: economic and social problems, declining population health levels, an increase in infectious diseases, a lack of interest on the part of employers in the donation of their employees in the context of the migration of employees from the public sector to private companies, weak promotion of donation and irrational use of the country's donor potential, in particular the limited operation of mandatory social and government programmes that should help to stimulate the blood-forming function and metabolism in the donor's body [6, 8].

It is known that, in the case of significant blood loss as well as the violation of the regulated number of donations during the year and a lack of careful monitoring of metabolic processes in the donor's body, donors may experience disorders of macro- and microelements, amino acid, protein, carbohydrate metabolism, and enzyme systems, which ultimately leads to the formation of deficiency conditions and disease states in regular blood donors [9]. These changes causing donors to withdraw from donation due to haemoglobin levels are mainly described in the literature as a consequence of unregulated donation. The effects of haemoglobin deficiency are related to disturbances in the metabolism of iron and trace elements ensuring adequate haemoglobin synthesis and erythropoiesis and in the functioning of metal-dependent enzyme systems and related metabolic processes [10].

Equally important, but often overlooked, are the psychological and social aspects of giving blood. Donors may feel anxious or stressed about the process of donating, and a lack of guidance on nutrition and recovery can exacerbate these feelings. Providing comprehensive information and support can improve the donor experience and make individuals more likely to return and donate again. Promotion of the benefits of proper nutrition and post-donation care can therefore foster a sense of community and shared responsibility, as donors realise that their contribution is not just a single act but part of a wider ongoing effort to save lives. Addressing these multifaceted aspects of blood donation can improve both donor satisfaction and overall programme effectiveness [8].

Several studies have investigated indicators that characterise iron metabolism in the donor's body and the condition of peripheral blood erythrocytes as a function of donor experience, the effect of collection methods and storage conditions on the quality of fresh frozen plasma, the health status of donors at different stages of plasma donation, the quality of fresh frozen plasma, etc. [11, 12, 13, 14]. Maintenance of donor health requires good

nutrition, as blood donors are at increased risk of iron deficiency [15, 16, 17]. Iron deficiency without anaemia and iron deficiency anaemia are potential harms to regular blood donors; therefore, maintaining donor health is no less important than ensuring a safe and continuous blood supply [14]. However, the problems of optimising donation through donor nutrition and its medical and social aspects are not yet fully understood.

Thus, while much emphasis is placed on the act of donating blood, less attention is paid to the preparation and post-donation care, particularly from a nutritional perspective. Ensuring optimal health of blood donors before and after donation is critical for maintenance of a safe and robust blood supply. Such factors as diet, hydration, and general health have a significant impact on the quality of donated blood and the recovery time of donors. A better understanding of these factors can help to mitigate potential adverse effects and encourage more frequent and reliable donations [19].

Using key terms such as "blood donation", "blood donor nutrition", "nutrient effects" on "blood donors" and "iron deficiency", this study aims to explore the relationship between diet and blood donation. The research focuses on the role of appropriate dietary practices in supporting the health of blood donors, addressing concerns such as iron deficiency and the effects of essential nutrients. The ultimate goal is to promote safe and informed blood donation, while allaying common fears associated with the process. The aim of this article is to provide a comprehensive overview of the effect of diet on the health and performance of blood donors addressing their nutritional needs, explaining the underlying molecular mechanisms, and providing practical recommendations to support the well-being of donors and the effectiveness of blood donation programmes worldwide. The review was based on search of the PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library, ScienceDirect databases. Elucidation of the key differences between a modern diet and a diet tailored specifically for blood donors is essential to understanding the purpose of this article. By highlighting these differences, we aim to emphasise the importance of a nutrient-dense diet for blood donors, which is critical for effective recovery and overall health maintenance. This explanation forms the basis of the article and highlights the significant impact of a targeted dietary approach on the well-being of individuals who donate blood on a regular basis.

The objective of this study is to investigate the relationship between nutrition and blood donation, with a particular focus on the nutritional needs of blood donors and the impact of nutrients on their health. Key aspects include addressing iron deficiency and providing evidence-based dietary recommendations to support safe and informed blood donation practices. In this way, we aim to encourage more people to donate blood while allaying concerns about potential risks.

Health, nutrition, and blood quality

The importance of blood donation cannot be overstated, as it is a critical component of healthcare systems worldwide, ensuring that life-saving blood and blood products are available to patients in need. Despite its importance, the specific nutritional needs of blood donors remain an under-researched area, often overlooked in both scientific research and public health discussions [13]. Blood donors face unique nutritional challenges, particularly in replenishing iron and other essential nutrients lost during donation. Understanding the impact of nutrition on donor recovery and performance is critical to optimising donor health and ensuring the sustainability of blood donation programmes [18]. This knowledge gap requires focused attention and thorough research to provide clear guidance and support to donors.

The main differences between a modern diet and a diet tailored specifically for blood donors lie in their goals and nutrient focus, as shown in Fig. 1. Modern diets often prioritise convenience, taste, and availability, often leading to high consumption of processed foods and sugary drinks that are low in essential nutrients. In contrast, a blood donor's diet is carefully

designed to support overall health and facilitate recovery after donation by emphasising nutrient-rich foods. This includes increased intake of iron-rich foods, such as lean meats and leafy vegetables, to replenish blood stores and vitamins A, C, and E to support cell repair and antioxidant protection [17]. In addition, a blood donor's diet should ensure adequate intake of essential minerals, such as zinc and copper, which are critical for immune function and red blood cell production, as well as proper hydration and avoidance of processed foods to ensure the diet provides all necessary nutrients without excess harmful additives [14, 20].

The physiological requirement for iron is relatively low, but in the event of acute or chronic blood loss, iron requirements increase. Iron is essential for normal erythropoiesis and enters the bone marrow in the following ways: during the destruction of red blood cells, from the depot, and with food and water. The daily diet of an adult must contain 12-15 mg of iron for normal erythropoiesis and for diets providing 18 mg iron/2000 kcal, according

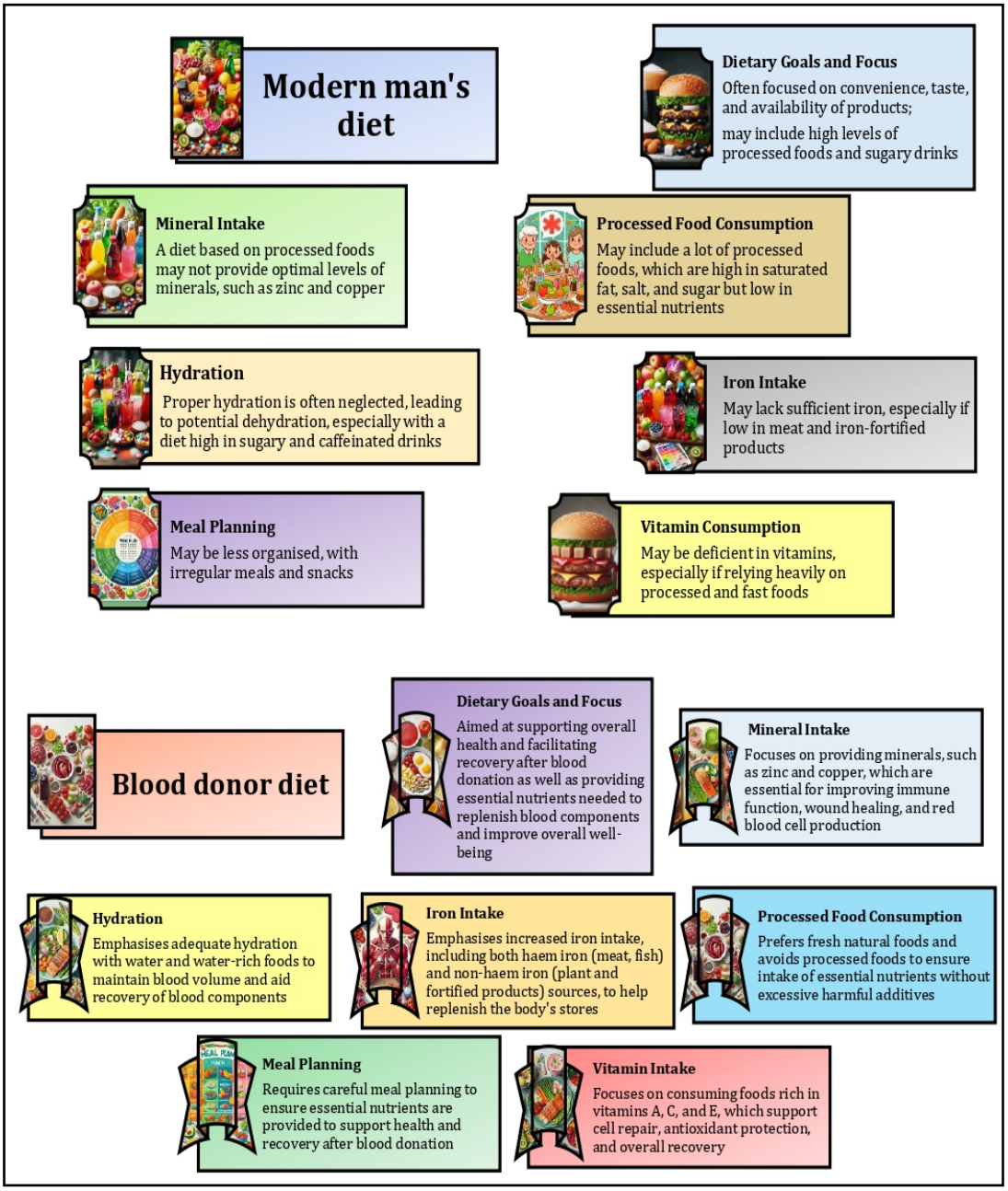

Fig. 1. Main differences between a modern diet and a diet for blood donors.

to the Recommended Dietary Allowances for iron and energy for women aged 23-50 years [21]. Reference Daily Allowances (RDAs), i.e. the average daily intake of nutrients for healthy people to meet their dietary needs, have been established by the Food and Nutrition Board, Institute of Medicine (IOM) as shown [22, 23]. In addition, an average intake (AI) for iron has been established for infants from birth to 6 months of age, corresponding to the average iron intake of healthy breastfed infants. According to the IOM, the AI for infants aged 0-6 months and the RDA for infants aged 7-13 months are 0.27 mg/day and 11 mg/day, respectively. For children aged 1-3 years, 4-8 years, and 9-13 years, the values are 7 mg/day, 10 mg/day, and 8 mg/day respectively. For adolescents (14-18 years), the RDA is different for boys and girls. While the RDA for male adolescents is 11 mg/day, the RDA for female adolescents is 15 mg/day. For adults aged 19 and over, the RDA is 8 mg/day for men and 18 mg/day for women. In addition, the RDA is 10 mg/day for lactating women under 18 years of age and 9 mg/day for women over 18 years of age. The RDA for vegetarians also varies. The RDA for a vegetarian male is 14 mg/day; in turn, the RDAs for vegetarian females aged 14-18, 19-50, and over 51 are 26 mg/day, 14 mg/day, and 33 mg/day respectively. Iron deficiency occurs when the body's iron needs are not met, which may lead to health problems [22].

Normally, iron in the body is in a dynamic equilibrium [24]. Of the approximately 10 mg of dietary iron, 1-2 mg is absorbed by duodenal enterocytes. In the circulation, iron is bound to transferrin (about 3 mg), which safely transports it to the bone marrow for haemoglobin synthesis. About two-thirds of the body's iron is found as haemoglobin in red blood cells (1800 mg) and erythrocyte precursors in the bone marrow (300 mg), while 10-15% is found in myoglobin and various enzymes. Iron is stored in parenchymal liver cells (about 1000 mg). Reticuloendothelial macrophages temporarily store iron recovered from senescent erythrocytes (600 mg) in a readily available form [24, 25]. Erythropoietin, produced by the kidneys, regulates iron absorption in the duodenum and erythropoiesis. In the human body, iron is a component of almost 70 important enzymes [26]. As suggested by Waldvogel-Abramowski et al. [27], the dietary intake of iron in a typical European diet is about 15 mg, of which only about 10% is absorbed, as absorption occurs via complex mechanisms mainly in appropriate regions of the gastrointestinal tract, especially in the duodenum and proximal jejunum [28].

There are two types of iron found in food, including haem iron and non-haem iron [29]. Haem iron is found exclusively in animal products, such as meat, fish, and poultry, whereas non-haem iron is found in fruits, vegetables, dried beans, nuts, and cereal products [30]. Haem iron is more efficiently absorbed from the gut than non-haem iron [31, 32]. Strict control of dietary iron intake is essential to maintain iron levels within the normal range and reduce the risk of iron deficiency. Iron absorption has been shown to be 25-30% with innards, 7-9% with green leafy vegetables, 4% with cereals, and 2% with dried pulses, suggesting that the type of food or other dietary factors may affect iron bioavailability [33]. For example, ascorbic acid is a known dietary factor that improves iron bioavailability [34], whereas calcium, polyphenols, phytates, and oxalates reduce iron absorption in the gut [35, 36]. Therefore, the type of foods in the diet should be considered to maintain iron balance in the body (Fig.1).

Consideration of the nutritional adequacy of iron highlights the importance of assessment methods, particularly the usefulness of the 'bioavailable nutrient density' approach to different meals [37]. The total body iron content is approximately 4.5-5 g, with 75-80% of iron in haemoglobin, which carries oxygen to tissues and 5-10% of iron in the blood. 5-10% is part of myoglobin, and 1% is part of respiratory enzymes that catalyse respiratory processes in cells and tissues. 20-25% of iron in the body is reserve iron. The physiological loss of iron in urine, sweat, faeces, hair, and nails is about 1 mg/day, independent of age and sex. In women with a normal menstrual cycle lasting 3-4 days, iron losses are about 15 mg (30-50 ml of blood). In hyperpolymenorrhoea (up to 50-250 ml of blood), iron losses increase significantly. During pregnancy, labour, and lactation, up to 1700-1800 mg of iron is lost [38].

The body loses approximately 1-2 mg of iron per day through sloughing of enterocytes and skin, bleeding, and parasitic invasion. As there is no active mechanism for iron excretion,

iron homeostasis requires daily intestinal absorption of 1-2 mg of iron. This requirement increases in physiological conditions, such as growth, pregnancy, and menstruation. Meanwhile, about 25 mg of iron is processed daily by macrophages of the reticuloendothelial system through phagocytosis of ageing red blood cells. This means that the majority of human iron homeostasis depends on iron recycling [27, 39]. Therefore, when there is an increased demand for the element, its deficiency is compensated by depleting reserves and then transporting resources. In celiac disease (gluten enteropathy), iron and B_{12} deficiency anaemia is also found in combination with malabsorption of other nutrients [40].

Diet has an impact on the quality of donor's blood. A balanced diet rich in essential nutrients, such as iron, vitamin B_{12}, and folic acid, is essential for the production of healthy red blood cells. Iron is needed for the production of haemoglobin, which carries oxygen in the blood. Iron deficiency can lead to anaemia, which can disqualify a donor [17].

Psychological and emotional aspects also play an important role in the long-term health of blood donors. Regular blood donation can provide psychological benefits, such as a sense of altruism and satisfaction from helping others [41]. However, some people may experience stress or anxiety associated with the blood donation process. It is important to monitor the diet for nutrients that may affect mood, such as omega-3 fatty acids, B vitamins, magnesium, and tryptophan. These nutrients play a role in the production of neurotransmitters, e.g. serotonin, which regulate mood and stress levels. Social support from family, friends, and medical staff as well as an appropriate diet can make a significant difference to the emotional well-being of donors and ensure that they remain physically and emotionally healthy in the long term [6, 8, 12].

Therefore, maintaining the health and nutritional status of donors is critical to ensuring the quality of donated blood [42]. Regular health checks and monitoring of medical parameters of donors help to eliminate potential risks associated with blood-borne diseases, which has a direct impact on the safety of recipients [43]. A balanced diet rich in vitamins and minerals supports the body's recovery after blood donation and ensures that donors can provide high quality blood [44]. Iron is particularly important, as it is essential for the production of haemoglobin, i.e. the protein in red blood cells that carries oxygen. Adequate iron levels prevent anaemia and ensure that donors remain healthy and able to donate regularly [14]. Education on healthy lifestyles and medical support for donors are essential to maintain their ability to donate regularly, which is fundamental to an effective blood donation system [42].

Prevention of adverse physiological reactions in blood donors

Blood donation is important for ensuring that life-saving blood and blood products are available to patients in need. Giving blood can be stressful for some people, especially first-time donors or those with a fear of needles. The rapid withdrawal of blood during donation can cause a temporary reduction in blood volume, which can trigger a vasovagal response [45]. A vasovagal reaction (VVR) is a common type of fainting or syncope that can occur in blood donors as a result of an autonomic nervous system reflex [46, 47]. VVR is a general feeling of discomfort and weakness with anxiety, dizziness, and nausea, which can progress to loss of consciousness [48]. This reaction can cause a sudden drop in the heart rate and blood pressure, leading to reduced blood flow to the brain and fainting [50]. Before fainting, a donor may experience light-headedness or dizziness, nausea, sweating, blurred vision or spots in front of the eyes, ringing in the ears, a feeling of warmth or flushing, weakness, paleness, and slow or irregular pulse [45, 50]. Non-hypotensive hypovolemia, such as that observed with blood donation, leads to a reflex readjustment of cardiac autonomic tone [49]. VVRs are generally benign, but they can be distressing for the donor and require the attention of medical staff.

VVR is fairly common, with rates varying between 2-5% among donors, depending on such factors as age, gender, and donation history [45, 50]. The risk factors for VVR include young age (under 30), first-time donor, low body weight, and anxiety, all of which increase the likelihood of experiencing a VVR [48]. Most vasovagal reactions are self-limiting and resolve without long-term consequences. However, donors who experience a severe reaction may be reluctant to donate again [45, 50]. Reassurance and education about prevention can help them to feel more comfortable returning for future donations.

Frequent blood donations can lead to lower iron levels, which can cause anaemia [51, 52]. The molecular mechanisms underlying the absorption of iron and the process of its recovery by the body after blood donation are complex and not fully understood [53]. Each donation is associated with a significant loss of approximately 200-250 mg of the functional iron pool in the donor's body, representing approximately 30% of the average body iron stores (BIS) in men and nearly 80% in women [51, 54]. It may lead to a high incidence of subclinical iron deficiency in long-term donors, affecting both women and men [14, 52]. Iron is stored in the form of ferritin (easily mobilised reserve) or haemosiderin (difficult to mobilise reserve) [55]. Plasma transport includes transferritin iron and accounts for about 1% of iron in the body [27]. Iron supplied by enterocytes (5%) and released by recycling of old red blood cells with the participation of mononuclear macrophages (95%) is mainly transported to the bone marrow [56].

Excessive iron intake leads to the formation of its specific biochemical form that can generate free radicals, which have been shown to cause complications [57]. Iron overload has been associated with oxidative stress in organs and tissue damage [58, 59, 60]. In this scenario, luminal iron may interfere with the mucosal barrier and its functions or create a harmful environment in the gut, inducing stress in epithelial cells. Some authors have suggested that elevated liver iron levels due to dietary iron overload may be associated with structural changes in the cecal mucosa [61, 62]. A study by Lobo et al. [57] suggests that these changes in the cecal mucosa may result from oxidative stress caused by excess iron in the intestinal lumen. These effects have significant consequences for intestinal absorption and implications for liver iron homeostasis.

Excessive amounts of iron in food or drug therapy over a period of days can lead to reduced iron absorption. This phenomenon, known as 'mucosal blockage', can be observed even with iron depletion. Excess iron can be observed in haematological patients after repeated blood or erythrocyte transfusions. Teams of authors provide a comprehensive review of the mechanisms and implications associated with the phenomenon of reduced iron absorption due to excess iron intake, namely 'mucosal blockage'. Each study covers different aspects of iron metabolism, from molecular regulation to clinical implications and effects on the gut microbiota [63-65].

Modern ferrokinetic studies have shown that, with a standard blood donation of 450 ml, a donor loses approximately 250 mg of iron from the functional iron pool [54, 66]. Given that 1 ml of red blood cells contains 1 mg of iron, it can be calculated that the iron loss from the apheresis methods of red blood cell collection is equal to or greater than that from whole blood donations. It can be argued that a regular blood donor loses between 500 and 1000 mg of iron per year. Due to the physiological characteristics of the female body, female blood donors are more susceptible to iron deficiency [67]. For example, a study by Prados Madrona et al. [68] on the role of women in altruistic blood donation in Huelva, a province in south-western Spain, showed that women are more altruistic than men in donating blood; a higher percentage of donors and first-time donors were observed among women. However, women also have more difficulties donating blood and are more prone to vasovagal reactions, which negatively affect their donor experience.

A recent study by Schreiber et al. [67] showed that regular blood donation affects ferritin levels differently in men and women. In women, frequent donation leads to higher ferritin levels, possibly due to increased iron absorption and the older age of frequent donors. In men, frequent donation leads to lower ferritin levels, indicating a greater depletion of iron stores. Age plays an important role in modulating these effects, with adjustments for age altering the

observed differences in ferritin levels. Anaemia indicators suggest that new female donors are more prone to anaemia, while frequent donation appears to reduce this risk, highlighting the body's adaptive response to regular blood loss. In the case of men, anaemia remains rare even among frequent donors, highlighting the importance of understanding gender-specific responses to blood donation for effective donor health management [67].

It is difficult to formulate effective dietary recommendations for blood donors without a full understanding of these mechanisms. To improve the health of donors and ensure that they can continue to donate safely and regularly, it is essential to fill these knowledge gaps. By shedding light on these critical issues, one can improve donor well-being, increase the efficiency of blood donation, and ultimately support the wider healthcare system. Intake of appropriate meals before giving blood helps to prevent weakness and dizziness that may occur during or after donation. Meals rich in complex carbohydrates, protein, and healthy fats stabilise blood glucose levels and provide the energy needed to maintain well-being during the donation process [69].

Therefore, in addressing the challenges of preventing fainting and dizziness in blood donors, it is important to recognise that women have more difficulty donating blood and are more susceptible to vasovagal reactions. This increased susceptibility has a negative impact on their donor experience [63]. Adequate iron levels play a critical role in this context, as iron is essential for the production of haemoglobin. Ensuring that donors, particularly women, have adequate iron levels through diet or supplementation can significantly reduce the risk of vasovagal reactions. Targeted strategies to mitigate these reactions, particularly in female donors, need to be implemented to improve donor retention and the overall donor experience. Improved donor education, proper hydration, and supportive care during and after donation as well as monitoring and management of iron levels can help to reduce the incidence of vasovagal reactions and ensure a more positive experience for all donors.

Iron content and sex hormones

The differences in iron levels between men and women are largely influenced by sex hormones, which regulate iron metabolism through a number of specific mechanisms. These differences can be attributed to the action of oestrogen and testosterone, which have different effects on iron homeostasis. The role of oestrogen in iron metabolism depends mainly on the regulation of oestrogen and hepcidin and on menstrual blood loss [70]. Lehtihet et al. [71] have shown that oestrogen down-regulates the expression of hepcidin, a key hormone produced by the liver that regulates iron homeostasis. Hepcidin controls iron absorption by binding to the iron exporter ferroportin on enterocytes in the gut and macrophages, leading to its degradation and reducing iron export into the bloodstream [72]. Lower hepcidin levels in women, especially premenopausal women, result in increased ferroportin activity and increased absorption of dietary iron and mobilisation of stored iron [73]. On the other hand, the regular menstrual cycle in women leads to periodic blood loss, which significantly affects iron levels. Therefore, oestrogen regulation of hepcidin is crucial to adapt to this regular iron loss by increasing intestinal iron absorption to compensate for the loss [74].

Testosterone stimulates erythropoiesis by increasing erythropoietin production in the kidneys and promoting the differentiation of erythroid precursor cells in the bone marrow [75]. This results in higher haemoglobin levels and red blood cell counts in men, contributing to greater overall iron demand and utilisation [76]. Testosterone also suppresses hepcidin production, similar to oestrogen, but through different signalling pathways [77]. This suppression facilitates increased iron absorption and mobilisation to support higher erythropoietic activity in men. As a result, men generally have higher serum ferritin levels than women [78].

Differences in iron absorption and storage have also been shown to be associated with important sex-related differences in iron metabolism [79, 80]. The efficiency of iron absorption in the gut differs between men and women and is influenced by different levels

of sex hormones. The effect of oestrogen in reducing hepcidin and increasing ferroportin activity results in a more dynamic adaptation to iron loss and demand in women [74]. Men maintain a steady state of higher iron absorption efficiency because they have consistently lower hepcidin levels due to testosterone [81]. Ferritin, the primary intracellular iron storage protein, is also subject to sex-specific regulation. The hormonal influence on hepcidin levels affects iron storage capacity in the liver, spleen, and other tissues [82]. Due to their higher erythropoietic activity and steady iron absorption rates, men tend to store more iron in ferritin [83].

A study by Stangerup et al. [66] focused on the menstrual cycle-influenced recovery period to investigate the effects of blood donation on exercise performance in women. Specifically, the study aimed to identify changes in VO_2peak, time trial performance, and haematological variables in 18 iron-sufficient women with plasma ferritin > 30 μg/L following a standard 450 mL blood donation. The results showed that the VO_2peak and blood haemoglobin levels did not return to baseline until 28 days after donation, whereas the time trial performance recovered within 14 days. This suggests that, while the overall physical performance measured by the time trial can recover relatively quickly, the full recovery of aerobic capacity and haemoglobin levels takes longer, highlighting the need for tailored recovery protocols for female donors, particularly those who menstruate [66].

It was noted that gender-specific recommendations for donor nutrition are essential to address the different physiological needs of male and female donors. Women are at higher risk of iron deficiency due to menstruation and should prioritise iron-rich foods such as lean red meat, beans and fortified cereals, along with vitamin C to enhance iron absorption. Men, while generally having higher baseline iron stores, should still ensure adequate nutrient intake to maintain optimal recovery and overall health after donation.

In summary, the interaction between iron content and sex hormones, such as oestrogen and testosterone, has significant implications for blood donors. Oestrogen in women can lead to lower iron levels due to menstrual blood loss, making female donors more susceptible to iron deficiency and related complications during donation. On the other hand, testosterone in men tends to support higher iron levels, which may explain why men generally have fewer problems with iron deficiency during the donation process. Understanding these hormonal influences is crucial for developing targeted strategies to manage iron levels in donors and ensure that both male and female donors maintain adequate iron stores. This approach will enhance donor safety and improve the overall donation experience, contributing to a more reliable blood supply.

Faster recovery from blood donation

Proper nutrition after giving blood is a key to a speedy recovery [84]. Meals rich in protein support tissue repair, while carbohydrates help to restore energy levels quickly. Hydration is also important to maintain adequate fluid levels in the body, which helps to return to normal more quickly after blood donation [85]. Intake of appropriate meals before giving blood helps to prevent weakness and dizziness that may occur during or after donation. Meals rich in complex carbohydrates, protein, and healthy fats stabilise blood glucose levels and provide the energy needed to feel good while donating [86]. Inclusion of a variety of nutritious foods in the diet means consumption of a wide range of foods that are rich in essential vitamins, minerals, and other nutrients but relatively low in calories and unhealthy additives [87, 88].

For blood donors in particular, this approach ensures a balanced intake of nutrients needed for optimal health and recovery. For example, inclusion of iron-rich foods, such as lean meats, legumes, and dark leafy greens, helps to replenish iron stores, while consumption of fruits and vegetables rich in vitamins A, C, and E supports immune function and protects against oxidative stress [89]. In addition, intake of foods rich in minerals (e.g. zinc and copper), such as nuts, seeds, and whole grains, supports wound healing and red blood cell production [90-92]. By diversifying their food choices and emphasising whole unprocessed

foods, individuals can maintain a healthy diet that supports their general well-being as well as the specific needs associated with blood donation. This is illustrated in Fig. 2.

A study by Hallberg and Rossander-Hultén [93] revised iron requirements for specific population groups, indicating that adult women require 2.84 mg of absorbed iron per day, while adolescents require 3.21 mg per day. These requirements are based on the 95th percentile, meaning that they meet the needs of 95% of people in these groups. To translate these absorbed iron requirements into dietary requirements, the researchers made six

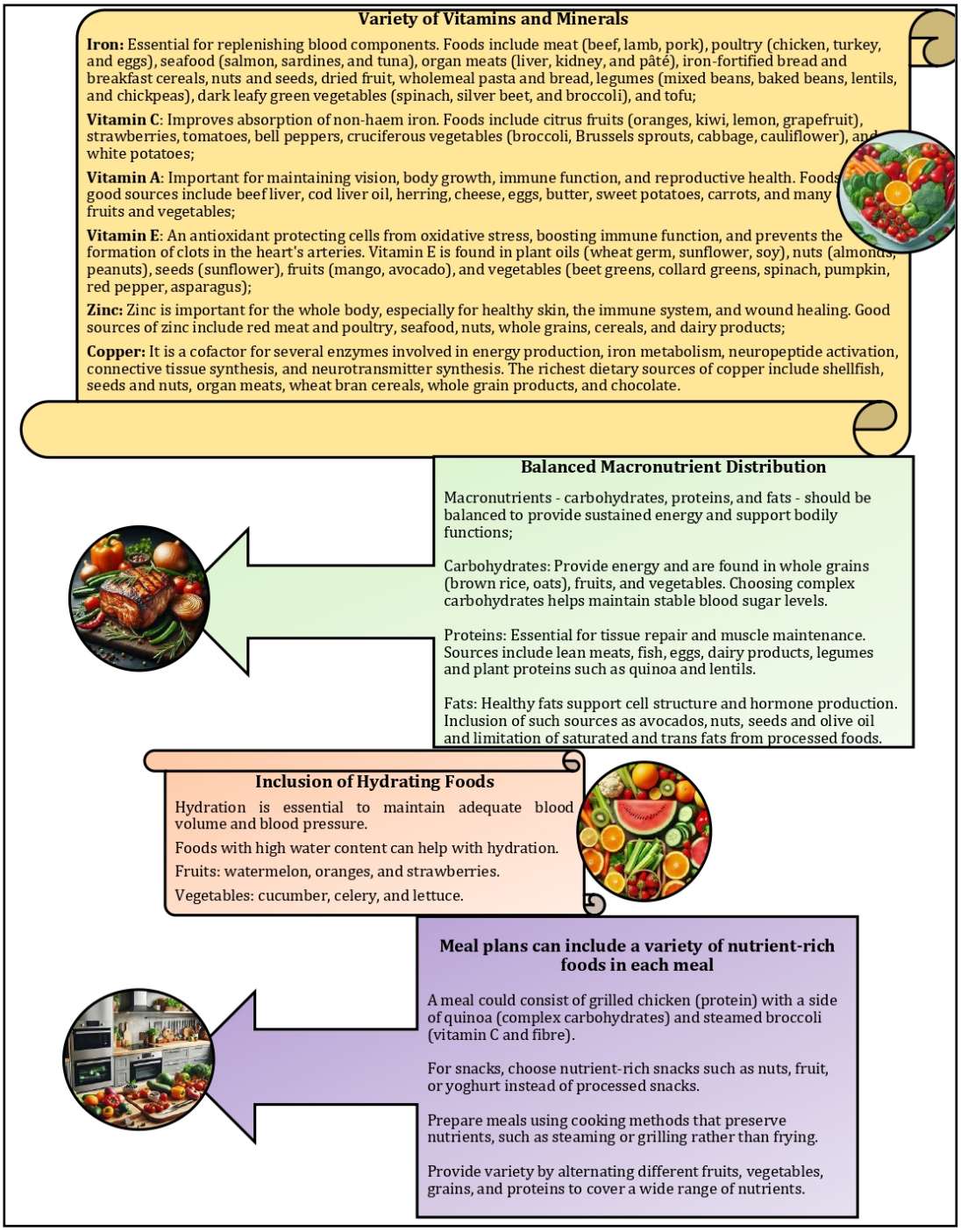

Fig. 2. Planning meals for donors aiming to include a variety of nutritious foods in the diet means inclusion of a wide range of foods that provide essential vitamins, minerals, and other nutrients while being relatively low in empty calories.

independent estimates of total dietary iron bioavailability and found that the bioavailability of iron in the Swedish, French, and US diets was 14%, 16%, and 16.6%, respectively. By averaging these results, 15% bioavailability was used to represent optimal long-term iron absorption from a typical Western diet. Another study looked at different dietary components that affect iron absorption, including enhancers such as vitamin C and inhibitors such as tannins, calcium, and phytates [36]. This study showed that tannic acid decreased the fasting bioavailability of non-haem iron; however, this effect was not present in the presence of calcium, and no effect of phytic acid or citrus pectin on the fasting bioavailability of non-haem iron was observed in the presence or absence of calcium [36].

Iron absorption occurs primarily in the duodenum and proximal jejunum and involves several mechanisms [94]. Haem iron is absorbed more efficiently than non-haem iron, with non-haem iron requiring reduction from ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron prior to absorption [95]. The hormone hepcidin, produced by the liver, regulates iron absorption by promoting the degradation of ferroportin, i.e. an iron exporter [29]. Based on bioavailability estimates, dietary iron requirements were calculated to meet absorbed iron needs: adult menstruating women need 18.9 mg per day, while menstruating adolescents need 21.4 mg per day. The study by Hallberg and Rossander-Hultén [93] highlights the importance of understanding both physiological iron requirements and the bioavailability of dietary iron, which is crucial for making accurate dietary recommendations, especially for populations at higher risk of iron deficiency, such as menstruating women and adolescents (Fig. 2).

Wiersum-Osselton et al. [96] investigated risk factors for vasovagal reactions and needle-related complications during blood donation, focusing on their impact on donor return. They found that first-time donation is an established risk factor for vasovagal reactions, which in turn negatively affects donor return rates. Interestingly, among first-time donors, women experienced fewer vasovagal reactions than men. Other risk factors in this study showed similar associations in both first-time and repeat donors. Regardless of whether donors were first-time or repeat donors, both vasovagal reactions and needle-related complications led to a decrease in subsequent donation rates, highlighting the importance of addressing these issues to maintain a stable pool of blood donors.

In summary, to facilitate faster recovery after blood donation, it is important to focus on incorporating a variety of nutritious foods into the diet to meet the absorbed iron requirement. Iron-rich foods should be prioritised to efficiently replenish iron stores. Examples of such iron-rich foods include a wide range of options. i.e. red meat (beef, lamb, and pork), poultry (chicken and turkey), fish and seafood (salmon, tuna, sardines, mussels, and clams), pulses (lentils, chickpeas, black beans, kidney beans, and soybeans), tofu, fortified cereals, dark leafy vegetables such as spinach, nuts and seeds (pumpkin seeds, sunflower seeds, and almonds), dried fruits (raisins, apricots, and prunes) and quinoa [97, 98]. In addition, combining iron-rich foods with those high in vitamin C, such as citrus fruits and peppers, can help to improve iron absorption [99]. By incorporating these dietary practices, donors can recover more quickly and maintain their overall health and willingness to donate in the future. This holistic approach not only supports individual donor well-being, but also helps to maintain a reliable and healthy donor pool.

Long-term health of blood donors

Blood donation involves the removal of a significant volume of blood from the body, which contains not only red blood cells but also essential nutrients, such as iron, vitamins, and minerals [100]. Proper nutrition before and after donation is essential to replenish these lost components and maintain donor health. Nutritional mechanisms therefore explain how a balanced diet rich in these essential nutrients supports the rapid recovery of blood donors, ensuring that they remain healthy and able to donate regularly [87]. Regular blood donation requires a healthy lifestyle, including proper nutrition. Healthy eating habits help to maintain appropriate haemoglobin levels and overall good health, allowing regular and safe blood donation [101].

The specifics of studying iron metabolism are crucial for understanding the recommendations for rapid rebuilding of the iron pool in long-term blood donors [100]. This detailed knowledge allows researchers and health professionals to determine the exact mechanisms by which iron is absorbed, transported, stored, and utilised in the body. It is well known that the special role of iron in biological systems is related to its ability to change its oxidation state over a wide range of oxidation-reduction potentials [102, 103]. This can be further modified by co-ordinated ligands. An extremely high level of iron enters the body, passes the rate-limiting absorption step, and becomes saturated. This free iron enters cells in the heart, liver, and brain. By interfering with oxidative phosphorylation, free iron converts ferrous iron to ferric iron, which releases hydrogen ions and increases metabolic acidity. Free iron can also lead to lipid peroxidation, resulting in severe damage to mitochondria, microsomes, and other cellular organelles, involving cellular oxidation and reduction mechanisms and their toxicity to intracellular organelles [104]. The hydrogen free radicals produced by iron attack DNA lead to cell damage, mutation, and malignant transformation, which in turn cause a range of diseases [105].

Living organisms have developed numerous mechanisms to tightly regulate the uptake, storage, utilisation, and export of iron. At the cellular level, the expression and translation of genes encoding proteins that modulate iron uptake, storage, utilisation, and export are regulated by iron regulatory proteins, sensors of intracellular iron levels, and post-transcriptional modifications. At the systemic level, the liver controls body iron levels by producing the peptide hormone hepcidin. Hepcidin reduces the amount of iron entering the bloodstream by blocking the function of ferroportin, the only iron exporter in mammals [106]. Cells have developed metabolic strategies to import and utilise iron safely. Regulation of iron uptake, storage, intracellular trafficking, and utilisation is critical for maintaining cellular iron homeostasis [107].

Iron is known to be involved in the Fenton reaction, which leads to the formation of the highly reactive hydroxyl radical and the formation of dinitrosyl iron complexes (DNICs) [108, 109]. *In vivo*, the two reactants of the Fenton-like reaction, the ferric citrate complex and H_2O_2, are readily available [108].The Fenton-like reaction of ferric citrate with H_2O_2 has been proposed as one of the mechanisms of the labile iron pool that can induce oxidative stress and cause pathological processes in the body [110, 111]. In addition, lysosomes also contain a redox-active iron pool derived from iron-rich macromolecules (ferritin) and cellular organelles (mitochondria) [112]. One of the possible sources of intracellular redox-active iron is the degradation of ferritin in lysosomes during autophagy [113] . The hydrogen peroxide that diffuses into lysosomes can react with the iron species through the Fenton and Fenton-like reactions, resulting in the generation of hydroxyl radicals [110].

Paramagnetic DNICs, discovered over 50 years ago as the first naturally occurring nitric oxide complexes in living organisms, may be a form in which iron ions are removed from most cells. Despite the tight control of iron levels and its storage as complexes with proteins, some iron is present in the cell in the form of a pool of iron labily bound to low molecular weight ligands that can readily undergo a Fenton reaction [114]. The increased production of nitric oxide and other radicals during oxidative stress is accompanied by an increase in the pool of labile iron as a result of its release from iron-sulphur cluster-containing proteins, such as aconitase or Rieske's protein [115]. At the same time, the iron contained in DNIC formed in cells is largely from the labile pool, and iron ions released from ferritin in oxidative stress conditions participate in the synthesis of DNIC with glutathione [116].

A number of molecular mechanisms involving aspects other than iron metabolism are engaged in the long-term health of blood donors. One key factor is blood regeneration, which requires the activation and proliferation of bone marrow stem cells [117]. Haematopoietic stem cells (HSCs) are a group of pluripotent stem cells found in haematopoietic tissues that can differentiate and produce a variety of mature blood cells (red blood cells, macrophages, platelets, lymphocytes, etc.) to maintain the normal physiological functions of living organisms [118]. Erythropoiesis is exquisitely regulated by an oxygen-sensing mechanism that has evolved to maintain the number of red blood cells within a narrow physiological range [119, 120]. Central to this mechanism is erythropoietin (EPO), a cytokine secreted by the kidney in response to low blood oxygen tension [121]. HSCs can also respond to infection

or injury by rapidly entering the cell cycle and differentiating, often preferentially along the myeloid lineage [122]. Additional insult-related signals may intervene to regulate the HSC fate in such dynamic conditions. It is known that both mature immune cells and HSCs can be activated either by direct activation of pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs), or by pro-inflammatory cytokine signalling [123, 124]. In addition, the bone marrow microenvironment, including lining cells, blood vessels, and extracellular matrix components, plays an important role in maintaining HSC homeostasis and function, which is critical for the health of blood donors [125].

Another important aspect of donor functioning is the immune system. Regular blood donation can stress the immune system [126]. Blood donors need to maintain a healthy immune system to prevent infections and other diseases, because T and B lymphocytes, which play a key role in the immune response, need to be constantly regenerated [127]. Such factors as interleukins (e.g. IL-2, IL-6, IL-7) are thought to be critical for the proliferation and differentiation of these cells [128]. In a study by Al-Hazimi [126], the stress on the immune system induced by the donation of 500 mL of blood was measured. The decrease in CD4+ cells (T helpers) and the increase in CD8+ cells (T suppressors) led to an imbalance, resulting in an overall decrease in the CD4/CD8 ratio. The CD8 lymphocyte subpopulation also has suppressive activity, which may have contributed to the decrease in CD4 cells. An increase in CD56+ (NK) cells was observed, which may indicate an improvement in the immune system. This may have been a result of a positive psychological effect that counteracts the stress. The stress induced by the blood donation also led to a significant increase in IgG, IgA, and IgM. Increased adrenaline levels may have triggered this increase in immunoglobulins to prepare the body's defence system to fight foreign invaders, such as bacteria, that may attack in stressful conditions [126].

Redox balance and oxidative stress within the donor cells are also important. Antioxidants, such as glutathione, and antioxidant enzymes, e.g. superoxide dismutase, catalase, glutathione-related enzymes such as glutathione reductase, and glutathione peroxidase, play a key role in protecting cells from oxidative damage caused by free radicals [129]. Dietary non-enzymatic antioxidants play an equally important role. Important non-enzymatic antioxidants for blood donors include vitamin C, vitamin E, glutathione, α-lipoic acid, coenzyme Q_{10}, uric acid, and α-carboxylic acid [130]. In excess, free radicals can be harmful. However, they have physiological roles in cell differentiation, immune cell activation, metabolic adaptation, and autophagy. It has therefore been proposed that their presence is not harmful and may contribute to maintaining health [131]. While an ideal antioxidant blend should reduce free radical levels, it is important to ensure that optimal levels of free radicals are present [130]. Therefore, monitoring and supporting these processes can help to maintain the long-term health of blood donors, minimise the risk of complications, and support overall immunity.

In addition to blood regeneration and immune system function, another important aspect of the health of long-term blood donors is cardiovascular health [132, 133]. Regular blood donation affects the volume of circulating blood, which in turn can affect haemodynamic parameters, such as blood pressure and heart rate [134, 135]. To maintain haemodynamic balance, the body activates compensatory mechanisms, such as changes in the activity of the renin-angiotensin-aldosterone (RAA) system and the secretion of antidiuretic hormone (ADH) as shown [136, 137]. It is also important to monitor the diet to ensure adequate intake of electrolytes, such as sodium and potassium, and nutrients that support cardiovascular health. A diet rich in vegetables, fruit, whole grains, healthy fats, and protein can help to maintain circulatory stability and healthy blood pressure [138]. The key to maintaining circulatory stability is the regulation of fluid and electrolyte volume [139]. Long-term blood donors should also maintain a healthy diet and regular physical activity to support cardiovascular health [140].

Importance of proper nutrition for blood donors

Good nutrition is the foundation of good health for blood donors. It not only ensures the quality of the blood donated, but also supports the donor's well-being and rapid recovery [141]. It is therefore important that donors pay attention to their diet and ensure that their body receives all the essential nutrients. At a molecular level, the absorption and metabolism of iron – a critical element in blood production – is highly dependent on dietary intake and overall nutritional status [103].

Lipemia, characterised by the presence of "opaque cloudy plasma", poses significant challenges to the production and use of blood components at the time of donation [142]. The presence of lipemic blood, resulting from various physiological and paraphysiological causes, metabolic disorders, common diseases, and certain medications, can complicate several aspects of transfusion medicine [143]. These difficulties include epidemiological, technical, analytical, clinical, and economic concerns. Due to the interference of lipemia with laboratory tests and the potential safety issues associated with the use of hypertriglyceridemic blood, most national and international guidelines discourage the use of lipemic donations for the production of blood components [144, 145]. While chemical or mechanical methods can reduce some assay interferences, the suitability of lipemic blood for clinical use remains unresolved. The prevalence of lipemic donations is generally between 0.31% and 0.35%, although some reports suggest it may be as high as 13% [146]. These two different types of donor plasma are shown in Fig. 3, with good quality plasma on the right and lipemic plasma on the left.

Fig. 3. On the left, the plasma is clear and transparent, indicating normal lipid levels in the blood. This is the desired state of plasma, allowing accurate laboratory testing and safe production of blood components. On the right, the plasma shows lipemia. The plasma is cloudy and milky in appearance, indicating high levels of lipids, particularly triglycerides, in the blood. This condition can occur for a number of reasons, including a high fat diet, metabolic disorders, or the use of certain medications. Before donating blood, donors should be instructed on proper dietary practices, especially avoiding fatty foods, to prevent lipemia. Regular monitoring of lipid levels and treatment of metabolic disorders may also help to reduce the incidence of lipemia. In transfusion medicine, it is important to develop and implement uniform guidelines for handling lipemic donations to ensure the safety and efficacy of blood and its components. Photo by Natalia Kurhaluk.

In addition, lipemia can sometimes lead to haemolysis of red blood cells, although this is less common. The presence of high levels of lipids in the plasma can cause physical changes or stress to red blood cells, potentially leading to their destruction. This haemolysis can further complicate the use of lipemic blood to produce safe and effective blood components [147]. Another study reported that there was no significant difference in haemolysis between erythrocytes from lipemic and non-lipemic whole blood donations when stored in saline-adenine-glucose-mannitol. The proportion of erythrocytes from lipemic donations with higher haemolysis was greater than in controls, so there was a weak correlation between erythrocyte haemolysis and plasma triglycerides [148]. The transfusion medicine community must work towards universal agreement and harmonised policies to effectively address the challenges posed by lipemic donations. This includes the formulation of clear guidelines and the adoption of consistent practices to ensure the safety and reliability of blood components derived from donations.

Iron bioavailability is the proportion of dietary iron absorbed in the gut and used for physiological functions, particularly haematopoiesis [29]. Absorption, i.e. the availability of iron for intestinal absorption, is sometimes used as a synonym for bioavailability, but good absorption is only one of the prerequisites for good bioavailability [149]. Bioavailability depends on the degree of absorption and the incorporation of absorbed iron into erythropoiesis [29]. Iron fortification of foods is considered the most cost-effective approach to reducing the prevalence of iron deficiency [150, 151]. The bioavailability of iron-based salts in the human body is in the following order: ferrous sulphate, ferrous lactate, ferrous fumarate, ferrous succinate, ferrous glycine sulphate, ferrous glutamate, ferrous gluconate > ferrous citrate, ferrous tartrate, ferrous pyrophosphate > ferric citrate, ferric sulphate [152]. Bioavailability can be improved by chelating iron using NaFeEDTA or ferrous glycinate, which improves luminal iron solubility [152].

There are two types of iron that can be found in food, i.e. haem iron and non-haem iron. Haem iron is only found in animal products such as meat, fish, and poultry. Non-haem iron is found in fruit, vegetables, dried beans, nuts, cereals, and meat [153]. The body absorbs haem iron more efficiently, but absorption of non-haem iron can be improved by intake of foods rich in iron absorption enhancers [29]. Ascorbic acid (vitamin C), folic acid, citric acid, peptides rich in the amino acid cysteine, and vitamin A are iron absorption enhancers [154]. Non-haem iron absorption can be enhanced by carotenes, retinoids, alcohol (by increasing gastric acid secretion, which promotes the valence state], and citric, tartaric, and malic acids [155]. Ferritin and transferrin play key roles in iron storage and transport, while hepcidin regulates iron balance by inhibiting absorption when iron levels are sufficient [156]. A healthy diet ensures that these molecular mechanisms function properly, supporting efficient blood production and recovery after donation; hence, a nutritious, well-balanced diet that includes iron-rich foods and foods rich in iron absorption enhancers is recommended for blood donors.

Furthermore, the long-term health of blood donors depends on a number of other mechanisms that involve aspects other than iron metabolism [157]. In blood donors, non-enzymatic antioxidants, including vitamin C (ascorbic acid), vitamin E (tocopherols and tocotrienols), glutathione, lipoic acid, coenzyme Q10 (ubiquinone), uronic acid, and α-carboxylic acid, play a key role in protecting cells from oxidative stress [158, 159]. Vitamin C is a powerful water-soluble antioxidant that protects cells from free radical damage, helps to regenerate other antioxidants such as lipid-soluble vitamin E, protects cell membranes from oxidative damage, and helps to protect lipids from oxidation [160]. Glutathione, a tripeptide consisting of glutamate, cysteine, and glycine, plays a key role in cellular detoxification and free radical scavenging as well as the regeneration of other antioxidants, such as vitamins C and E [161-163]. Lipoic acid is a potent antioxidant that acts in both oxidised and reduced forms to support the regeneration of other antioxidants and protect cells from oxidative stress, promoting energy metabolism and detoxification [164]. Coenzyme Q10, which is a fat-soluble compound, plays a key role in energy production in mitochondria and in

protecting cells from oxidative damage [165]. Uronic acid, a product of glucose metabolism, acts as an antioxidant by neutralising reactive oxygen species [166]. Alpha-carboxylic acid, found in several fruits and vegetables, helps to protect DNA and other biomolecules from oxidative damage [167]. A diet rich in these antioxidants may help to protect the health of blood donors by supporting their resistance to oxidative stress and improving their overall body condition.

Blood donors should focus on a balanced diet rich in tryptophan, tyrosine, omega-3 fatty acids, magnesium, and antioxidants in the days before donation, as this can help to prepare the body and mind, reduce anxiety, and improve mood [168-171]. A healthy breakfast or lunch prior to the donation should include protein (lean meat, cheese, and yoghurt), complex carbohydrates (bread, cereals, and fruit), and iron-rich foods (red meat, fish, poultry, beans, and raisins). After the donation, continuous consumption of a nutritious diet will support recovery and maintain emotional well-being, with hydration essential to prevent fatigue and maintain mental clarity [172]. Dietary recommendations before and after blood donation are shown in Figures 4 and 5.

Thus, proper nutrition of blood donors is therefore of paramount importance (Figs 1 and 2). Educating donors about eating a balanced diet, avoiding fatty foods prior to donation, and staying well hydrated can help to reduce the incidence of lipemia. Good dietary habits improve not only the quality of blood donations but also the overall health of donors and the efficiency of the blood donation process. Addressing lipemia requires a multifaceted approach that includes understanding its causes, managing its impact on blood component production, and emphasising the importance of proper donor nutrition. Establishing clear guidelines and harmonising policies worldwide can help to mitigate the challenges posed by lipemic donations, ensure the safety and reliability of blood components, and promote healthier donation practices.

Fig. 4. Dietary recommendations after blood donation consist of the following elements: iron-rich foods, foods rich in protein and complex carbohydrates, foods rich in vitamin C with iron-rich meals improving the ability to absorb of iron, adequate hydration products, and products to avoid after blood donation: alcohol and caffeinated beverages.

Fig. 5. Sample menus for the day after blood donation.

Iron metabolism

Iron in the body is conventionally divided into several categories that encompass the different forms and functions of this element [173]. These include functional iron, transport iron, stored iron, and free pool iron. Each of these forms of iron has specific functions and is essential for the proper functioning of the body. Maintaining a balance between the different forms of iron is essential for good health, and both iron deficiency and iron excess can lead to serious health problems. Iron is a vital micronutrient playing an essential role in many biological processes such as oxygen transport, DNA synthesis, enzyme function, and others. Its diverse functions lead to different classifications based on a number of criteria [174].

The main pools of iron in the body consist of haem (cellular), non-haem (extracellular), and iron stores (depots), as shown in Fig. 6. Haem (cellular) iron makes up a significant proportion (70-75%) of iron in the body. It is involved in internal iron metabolism and is part of haemoglobin, myoglobin, enzymes (cytochromes, catalase, peroxidase, NADH dehydrogenase), and metalloproteins (aconitase, etc.). Non-haem extracellular iron consists of free plasma iron and iron-binding serum proteins (transferrin, lactoferrin) involved in iron transport [175, 176]. Iron stores (depots) are present in the body in the form of two protein compounds, ferritin and haemosiderin, which are mainly deposited in the liver, spleen, and muscles. They are incorporated into metabolism in the event of cellular iron deficiency [177, 178].

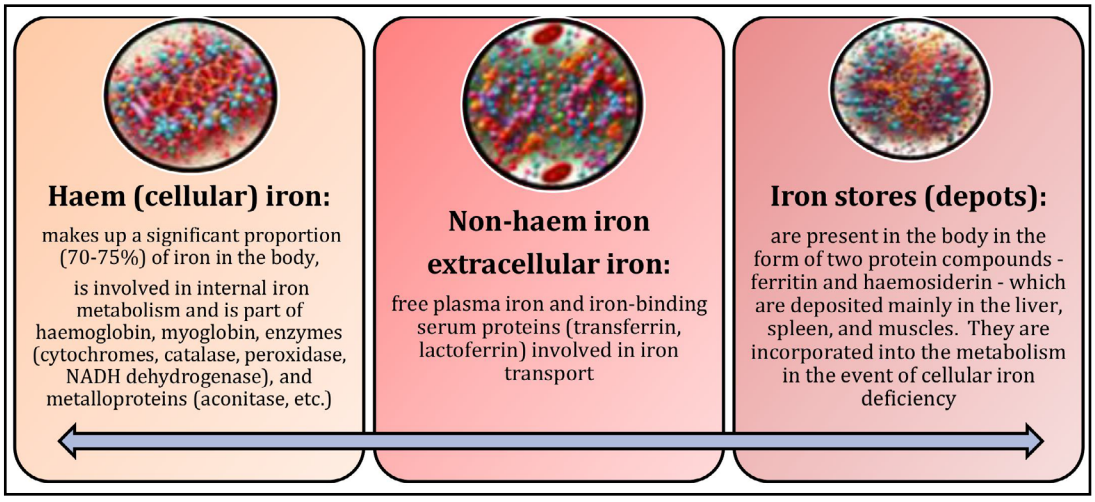

Fig. 6. Main pools of iron in the body.

As a result of these diverse functions, its role as functional iron, transport iron, storage iron, and free pool iron may vary depending on the research and clinical context (Fig. 7). Functional iron is directly involved in biological functions as part of key proteins and enzymes. Functional iron is associated with haemoglobin – a protein found in red blood cells responsible for transporting oxygen from lungs to tissues and carbon dioxide from tissues to lungs, and myoglobin – a protein found in muscles that stores oxygen and facilitates its rapid release during exercise [179].

Iron is transported throughout the body by transport proteins, such as transferrin, lactoferrin, and mobilferrin [181, 182, 185]. Transferrin is the major iron-transporting protein in the blood, binding free iron and delivering it to cells via the transferrin receptor [186]. Lactoferrin, i.e. a protein responsible for transporting iron within cells found mainly in milk and other secretions, binds iron and has antibacterial and immunomodulatory properties [183]. Stored iron is iron deposited in the body for use in times of deficiency or increased demand. The main forms of stored iron are ferritin and haemosiderin [184]. Ferritin acts as a protein that stores iron in the liver, spleen, and bone marrow and can release iron when needed, and haemosiderin is a form of stored iron formed when ferritin is overloaded with this element; it is less readily available for mobilisation than ferritin [55]. A small amount of iron circulates in the blood in a free, unbound form as free pool iron [180]. It is a highly reactive form of iron that can lead to the formation of free radicals; therefore, its concentration is tightly regulated by the body [103].

Coordination of iron homeostasis processes

Coordination of iron metabolism, particularly in donors, ensures balanced iron homeostasis, which is essential for proper cellular function [64]. Adequate iron supply supports critical biological activities, such as oxygen transport and energy production, while regulatory mechanisms prevent the potential toxicity of excess iron [103]. Research into these molecular mechanisms provides a deeper understanding of iron physiology and pathophysiology and may lead to better treatments for disorders associated with iron imbalance. Iron homeostasis relies on a complex network of proteins that manage the uptake, transport, storage, and regulation of iron in the body. At the forefront of iron absorption are divalent metal transporter 1 (DMT1) and ferroportin 1 (FPN1). DMT1, located on the apical membrane of intestinal enterocytes, is responsible for importing non-haem iron from the diet into enterocytes. Once inside these cells, iron can be exported into the bloodstream by FPN1, which is located on the basolateral membrane. This process allows entrance of iron to the circulation and its delivery to various tissues [187, 188].

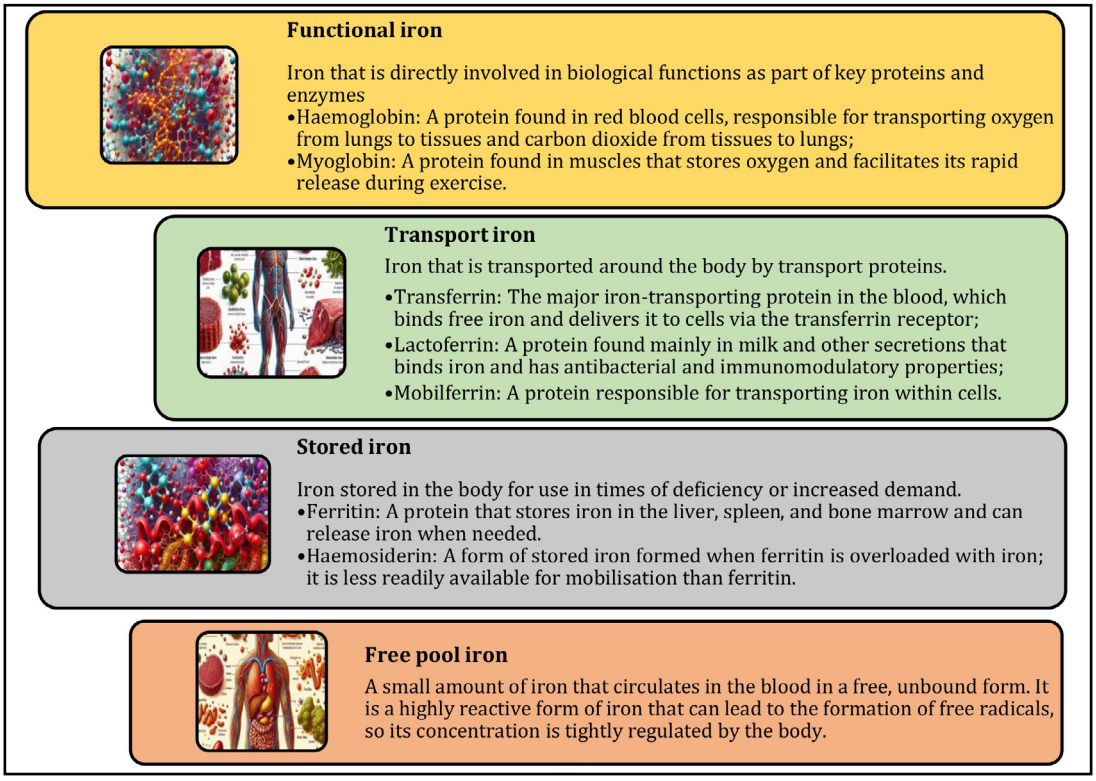

Fig. 7. Different forms of iron in the body.

Plasma transferrin carries iron around the blood, binding it so that it does not react with other molecules and cause damage. Transferrin transports iron to various tissues and cells where it binds to the transferrin receptor 1 (TfR1) on cell membranes. This binding facilitates endocytosis of the transferrin-iron complex into the cell. In the acidic environment of the endosome, iron is released from transferrin and enters the cytoplasm via DMT1 on the endosomal membrane. This iron can then be used in various metabolic processes, such as haemoglobin synthesis, or stored in cytosolic ferritin to prevent toxicity [189].

The regulation of iron homeostasis is primarily controlled by hepcidin, a peptide hormone produced by the liver [190]. Hepcidin binds to FPN1, causing it to be internalised and degraded, thereby reducing the export of iron from enterocytes and macrophages into the bloodstream. This regulatory mechanism ensures that dietary iron absorption and iron release from stores are tightly controlled to meet the body's needs without causing iron overload. In parallel, intracellular iron regulatory proteins (IRPs) modulate the expression of DMT1, TfR1, ferritin, and FPN1 by binding to iron responsive elements (IREs) in their mRNAs, thereby adjusting protein levels in response to intracellular iron concentrations [191-193].

Iron deficiency occurs when the amount of iron required by the body cannot be met due to a number of physiological consequences, including blood loss and limited dietary intake [190]. Hypoxic and sideropenic syndromes are the main clinical manifestations of iron deficiency anaemia [196]. The hypoxic syndrome has been shown to include symptoms common to all anaemias: pallor, paleness, palpitations, tinnitus, headache, and weakness [197]. Sideropenic syndrome manifestations include taste perversion, dry skin, nail changes, hair loss, angular stomatitis, burning tongue, and dyspeptic syndrome. The diversity of clinical manifestations of iron deficiency is due to the wide range of metabolic abnormalities resulting from the dysfunction of iron-containing and iron-dependent enzymes [103, 198]. Dietary interventions are the most appropriate way to improve iron status and can act as an alternative to conventional treatment [194]. The clinical manifestations of iron deficiency anaemia are shown in Fig. 8.

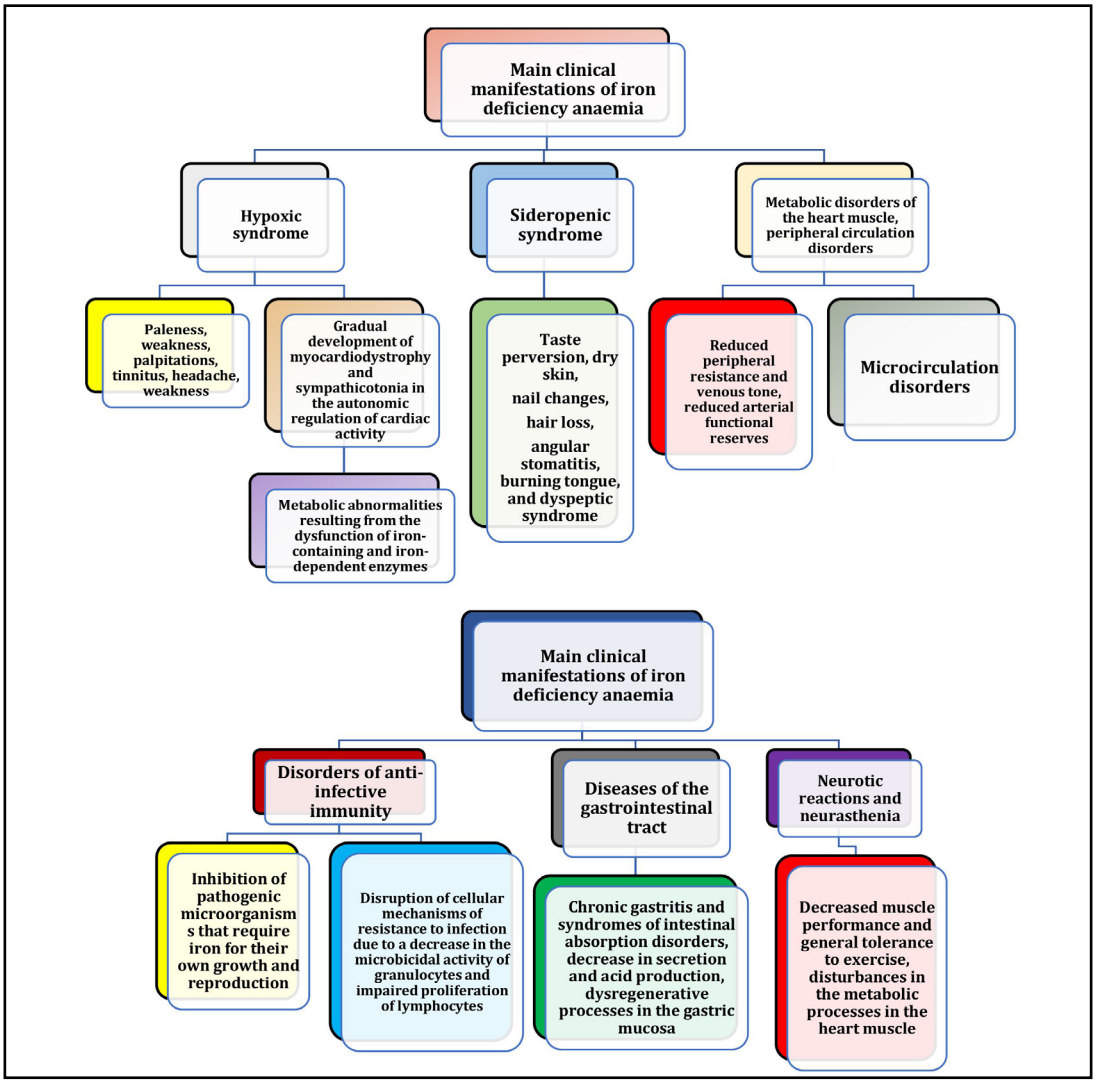

Fig. 8. Clinical manifestations of iron deficiency anaemia.

Less well known clinical manifestations of iron deficiency include neurotic reactions and neurasthenia, decreased muscle performance and general exercise tolerance, and disturbances in myocardial metabolic processes, peripheral circulation (decreased peripheral resistance and venous tone, decreased functional reserves of arterioles), and microcirculation. In the long-term course of iron deficiency anaemia, patients gradually develop myocardiodystrophy and sympathicotonia in the autonomic regulation of cardiac activity [13, 100, 199, 200]. In studies of iron deficiency anaemia, the main clinical manifestations of iron deficiency are lesions of the gastrointestinal tract, manifested as chronic gastritis and syndromes of intestinal absorption disorders [201]. At the same time, the decrease in secretion and acid production in chronic gastritis is considered to be a consequence rather than a cause of iron deficiency, and is explained by dysregenerative processes in the gastric mucosa [202]. It is thought that iron deficiency in the intestinal wall may lead to increased absorption and accumulation of toxic concentrations of iron antagonist metals in the body [203, 204].The disorders of anti-infectious immunity in patients with iron deficiency anaemia reported in the literature are complex in origin, involving inhibition of pathogenic microorganisms that require iron for their own growth and reproduction as well as disorders of cellular mechanisms of resistance to infection due to a decrease in the microbicidal activity of granulocytes and impaired proliferation of lymphocytes [205-207].

Iron compounds, nutrients, and food iron fortification

Iron bioavailability is the proportion of dietary iron absorbed in the gut and used for physiological functions, particularly haematopoiesis [29]. Absorption, i.e. the availability of iron for intestinal absorption, is sometimes used as a synonym for bioavailability, but adequate absorption is only one of the prerequisites for good bioavailability [208, 209]. Iron bioavailability depends on the degree of absorption and the incorporation of absorbed iron into erythropoiesis [210]. Food fortification with iron is considered the most cost-effective approach to reducing the prevalence of iron deficiency [150].

All iron compounds approved for use in foods can be divided into several groups: inorganic salts, organic acid salts, and chelates. The following iron compounds are approved for food fortification: ferrous gluconate, ferrous bisglycinate, ferrous carbonate, ferrous sulphate, ferrous lactate, ferrous fumarate, ferrous citrate, ferrous diphosphate (pyrophosphate), elemental iron (carbonyl + electrolytic + hydrogen reduced), ferric citric ammonium (ferric ammonium citrate), ferric orthophosphate, ferric succinate, ferric saccharate, ferric amino acid complexes, ferric sodium complex of ethylenediaminetetraacetic acid, and sodium ferric diphosphate [211, 212].

The interaction of iron and macronutrients in foods can cause oxidation of product components (lipids), resulting in organoleptic changes (off-flavours). Iron can also cause adverse colour changes by reacting with micronutrients (polyphenolic compounds found in tea, coffee, chocolate, and many fruits) [213-214]. The use of iron pyrophosphate, elemental electrolyte iron, and encapsulated iron, unlike other forms, does not affect the organoleptic performance of the product and does not cause gastrointestinal upset [215, 216]. Water-soluble iron salts have a higher bioavailability but also a greater ability to cause unacceptable changes in product properties [150]. This is because iron ions in solution have a distinct metallic taste; iron can form unacceptable coloured complexes with polyphenolic compounds and oxidise fats in lipid-containing products, such as wheat flour and whole or powdered whole milk [29, 150].

Several studies have looked at the relationship between iron and macronutrients in food [217-219]. The presence of sufficient amounts of iron absorption enhancers [ascorbic acid, fish, poultry, and meat, as found in most developed countries) overcomes the inhibition of iron absorption by even large amounts of tea [33]. Iron absorption may be a problem in individuals with low intakes of haem iron, low intakes of enhancing factors, and/or high intakes of inhibitors. Although depletion of iron stores increases iron absorption, this effect is not sufficient to compensate for inhibited absorption in such an inadequate dietary situation [29]. Studies by Andrews et al. [220] and Jaramillo et al. [36] have shown that calcium, phytic acid, polyphenols, and dietary fibre are major inhibitors of iron absorption and may be present in excess in some diets, thereby altering or modifying iron nutritional status. In addition, phytic acid combined with calcium is a potent inhibitor of iron absorption [220, 221]. Pectin, with or without calcium, was found to slightly reduce iron absorption. Tannic acid showed unexpected behaviour, inducing an increase in iron absorption despite its low ability to dialyse Fe [220].

For people at risk of iron deficiency, the study by Ma et al. [222] recommends increasing the intake of haem iron (this form of dietary iron, found in meat, fish, and poultry, is little influenced by other dietary factors in terms of its absorption). The transport of haem iron across intestinal enterocytes can be reduced by the small amounts of polyphenolic compounds present in food. However, the inhibitory effects of dietary polyphenols on haem iron absorption [223] can be counteracted by ascorbic acid and can be avoided by reducing polyphenol consumption and taking ascorbic acid at the same time [222]. Another recommendation is to increase ascorbic acid intake with meals and to fortify foods with iron. Recommendations for tea consumption (if in a critical group) include drinking tea between meals rather than during meals and consuming ascorbic acid and/or meat, fish, and poultry at the same time [222].

Ferrous sulphate, ferrous gluconate, ferrous fumarate, ferrous pyrophosphate, sodium ferrous ethylenediaminetetraacetic acid (NaFeEDTA), ferrous bisglycinate, and elemental iron powder are the most commonly used forms to fortify foods with iron [211, 224]. Ferrous sulphate and gluconate are soluble in water and gastric juice. Ferrous fumarate is poorly soluble in water but dissolves completely in gastric juice during digestion and is thought to have the same bioavailability as ferrous sulphate [225]. Ethylenediaminetetraacetic acid and bisglycinate are iron chelates with comparable absorption to that of ferrous sulphate in the absence of iron absorption inhibitors [225, 226]. As iron bisglycinate chelate is absorbed unchanged, there is no contact of free iron not only with the gastric mucosa but also with foods that inhibit iron absorption (dairy products, tea, coffee, etc.) [227]. This means that chelated iron can be used independently of dietary intake. Another important advantage of ferrous bisglycinate chelate is its higher bioavailability - almost four times higher than that of ferrous sulphate [228, 229]. This can be explained by the presence of two absorption pathways and binding to two types of receptors. The first type of receptor, DMT1, located in the duodenum, is for iron salts [230]. The second type of receptor, PEPT1, located throughout the small intestine, is designed to bind peptides. The presence of the amino acid glycine in the iron bisglycinate chelate allows it to bind to this type of receptor as well. As a result, the absorption of this compound is significantly increased [227].

It is known that iron is absorbed in the intestine in both ionic and complex forms as well as via the paracellular route. Fe^{3+} iron ions must first be reduced to Fe^{2+} by cytochrome b reductase or other reductases at the brush border membrane [231, 232] and by food components acting as reducing agents before being transported into enterocytes by the divalent metal transporter 1 [233]. Iron ions can form chelate complexes with other molecules, which are taken up by endocytosis and importers [232, 234]. It has been concluded that haem and iron bisglycinate have similar absorption properties [235, 236].

For this reason, food fortification with iron is considered the most cost-effective approach to reducing the prevalence of iron deficiency in blood donors [237]. Because of its cost-effectiveness, this strategy can be widely applied to at-risk populations, leading to significant improvements in public health. However, when implementing food fortification programmes, it is important to consider issues related to the dietary inhibitors of iron absorption [30]. These inhibitors can have a significant impact on the effectiveness of iron fortification; hence, addressing them is critical for ensuring that blood donors receive adequate levels of iron [29, 150, 210]. Addressing these factors can significantly reduce the rates of iron deficiency among blood donors, particularly in regions with high incidence of anaemia, with long-term health and economic benefits [237].

Key nutrients and their impact on blood donor well-being

Iron as main meal component

In healthy individuals, approximately 80% of absorbed iron is used for haemoglobin synthesis, where iron provides a specific binding site for oxygen in the haem moiety of haemoglobin in erythrocytes [103, 238, 239]. A whole blood donation results in the loss of approximately 225-250 mg of iron [240, 241], which can lead to iron depletion and a subsequent decline in haemoglobin levels if donations are frequent. Therefore, dietary iron intake is particularly important for blood donors to maintain iron homeostasis and haemoglobin levels as shown in Fig. 6-8. As suggested by Skolmowska and Głąbska [242], adult men and postmenopausal women should consume 10-11 mg/day of iron. Female blood donors have a much higher risk of iron deficiency anaemia than men due to menstrual blood loss. Iron loss in both women and men leads to iron deficiency and subsequent anaemia if the element is not replenished [243, 244]. The level of iron in the donor's body depends not only on the frequency of blood donation but also on many other factors, such as physiological factors, diet, or lifestyle [244]. It has been shown that age, body mass index (BMI), and alcohol or meat consumption are positively associated with iron levels in the body [245, 246], while age, gender, frequency of blood donation, and differences in lifestyle of donors can influence the level of haemoglobin in the blood [241].

Iron has been shown to be present in such animal products as beef, turkey (especially dark meat), chicken, lamb, pork, and fish [29]. Beef contains more total iron (2.2 mg/100 g) than veal (1.5 mg/100 g), lamb (1.5 mg/100 g), pork chops (1.0 mg/100 g), and chicken breast (0.9 mg/100 g). The iron content in meat from the same animal varies in different muscle groups; the iron content in red meat chicken legs (1.8 mg/100 g) is twice that of white meat chicken breast; duck meat contains 1.2 mg of iron/100 g, while duck breast has high iron content of 4.5 mg/100 g. Most minced beef comes from older dairy cows, which means it has high content of haem iron. Of the total iron content, haem iron accounts for 83% in beef, 63% in pork chops, and 33-44% in chicken [247]. Giblets and blood products such as black pudding contain high levels of haem and non-haem iron and meat factors. For example, the total iron content in pork offal is as follows: liver 13.4 mg/100 g, liver paté 5.6 mg/100 g, heart 6.0 mg/100 g, kidney 3.3 mg/100 g, and black pudding 16.2 mg/100 g. The total iron content in lean fish is 0.2 mg/100 g in cod, 0.1 mg/100 g in flounder, and 0.8 mg/100 g in sea bass. The content of this element in fatty fish is 0.2 mg/100 g in farmed salmon, 0.8 mg/100 g in mackerel, 0.7-1.3 mg/100 g in herring, and 1.6 mg/100 g in tuna. Cod fillet contains no haem iron, whereas 30-40% of the iron in other fish is haem iron. Fish flesh also contains meat factors; therefore, the iron contained therein has relatively good bioavailability [247].

Significant variations in iron content have been observed between different natural dietary sources, both animal and plant (Fig. 2). A study by Briguglio et al. [248] summarised the main natural sources of dietary iron and highlighted their potential contribution to human nutrition. Among animal foods, organ meats, especially liver, are particularly rich in iron. The presence of the non-haem-enhancing meat protein factor (MPF) may improve the absorption of this iron, as red meat is a relatively rich source of highly bioavailable haem iron, providing about 1.1-1.3 mg per 100 g, compared to chicken and fish, which provide about 0.1-0.9 mg per 100 g, while red meat contains higher levels of poorly bioavailable non-haem iron [249]. Raw veal and other mammalian livers have an impressive iron level of 20 mg per 100 g. This high concentration makes liver one of the most potent sources of dietary iron available. Chicken egg yolk and various types of raw fish both contain around 5 mg of iron per 100 g, making a significant but smaller contribution than liver. Raw meats, such as veal and beef, provide about 4 mg of iron per 100 g, which is substantial but still considerably less than organ meats. In contrast, cow's milk, a commonly consumed animal product, contains a negligible amount of iron, i.e. merely 0.2 mg per 100 g [248, 249] and shown in Figs 4-8.

In contrast, most dietary iron is in the form of non-haem iron, which is found in whole grain breads and pasta, whole grains, seeds, nuts, tofu, peanuts, kidney beans, lentils, oats, chickpeas, peas, couscous, dried apricots, almonds, spring greens (spinach, kale), and dried fruits (raisins, apricots, and prunes) as shown [97, 98]. Plant foods are also valuable sources of iron, although the bioavailability of non-haem iron from these sources can vary [248]. Dried common oregano is a top contender among plant foods, providing 18 mg of iron per 100 g. Bitter cocoa powder, often used in various culinary applications, provides 14.3 mg of iron per 100 g. Arabica coffee powder follows with 12 mg of iron per 100 g, highlighting its potential contribution to dietary iron intake, particularly in populations with high coffee consumption. Dried pulses such as lentils and beans are well known for their iron content, providing around 9 mg per 100 g. These foods are important sources of iron in many vegetarian and vegan diets. Similarly, wheat bran and soya flour, both dried, provide about 8 mg of iron per 100 g. Nuts, including walnuts, almonds, and pistachios, contain around 7 mg of iron per 100 g, making them a valuable addition to an iron-rich diet. Edible mushrooms, while not as rich in iron, still contribute between 1 and 2 mg per 100 g, and red wine provides a modest 0.9 to 1.1 mg of iron per 100 g, which can add up if consumed regularly [248, 249].

The absorption of non-haem iron is less efficient and more variable, with only 1-10% being absorbed [250], and is influenced by many dietary factors [153] and shown in Figs 7 and 8. Dietary iron is absorbed in the proximal small intestine. Men typically absorb about 1 mg/day, which corresponds to their basal losses mainly from the gastrointestinal tract. Premenopausal women absorb more, about 1.3-1.5 mg/day, due to additional menstrual losses [251]. The body's absorption capacity increases in response to iron deficiency,

reaching an average maximum of 4-5 mg/day in highly active blood donors, although the average absorption rate is more commonly 2-3 mg/day.51 Maintaining adequate iron levels is essential for blood donors. This is due to the significant iron loss associated with donation and the importance of both haem and non-haem iron sources in the diet [100].

It has been suggested that a higher intake of non-haem iron is associated with lower haemoglobin (Hb) levels, independent of haem iron intake. This is due to the presence of phytate and polyphenol-rich foods and beverages (such as legumes, cereals, and coffee), which inhibit the absorption of non-haem iron [103, 241]. Data show that blood donors with higher intakes of haem iron and lower intakes of non-haem iron tend to have higher Hb levels, a relationship mediated by higher ferritin levels [241]. The main sources of dietary iron are meat, poultry, and fish [29]. Haem iron from haemoglobin and myoglobin accounts for 40% of the total iron in animal foods and is much more efficiently absorbed (15-40%). In contrast, non-haem iron makes up all the iron in plant foods [252]. To effectively replenish iron stores and prevent iron deficiency anaemia, iron-rich products should be included in the diet of blood donors [14].

Vegetarians are at greater risk of anaemia than non-vegetarians because their diets lack or contain lower levels of highly bioavailable haem iron, and they often struggle to maintain haemoglobin levels required for repeated blood donations [253, 254]. In addition, certain compounds in plant foods inhibit the absorption of non-haem iron. To improve iron bioavailability, vegetarians are advised to increase their intake of vitamin C and other organic acids [242].

Thus, the literature highlights the importance of inclusion of both animal and plant foods in dietary planning and emphasises the diversity of natural dietary sources of iron [14]. Research into the bioavailability and absorption of iron from these diverse sources has informed and refined dietary recommendations and guidelines, increasing their effectiveness in preventing and treating iron deficiency. Organ meats, especially liver, have been identified as particularly rich sources of iron, while various plant foods, such as oregano and cocoa powder, also contribute significantly [29]. Understanding the iron content in these foods is important, particularly for those at risk of iron deficiency or requiring higher iron intakes, such as blood donors, pregnant women, and athletes. These findings highlight the need for careful dietary planning to ensure adequate iron intake from a variety of sources.

Influencers and inhibitors of iron absorption

Iron absorption is known to be influenced by the presence of various dietary facilitators and inhibitors [238, 255, 256]. By understanding the iron absorption pathways and their regulation, more effective dietary strategies and interventions can be developed to combat iron deficiency, especially in vulnerable populations [257]. These mechanisms highlight the importance of dietary sources of both haem and non-haem iron in maintaining adequate iron levels, particularly in populations at risk of iron deficiency, such as blood donors. Enhancing the bioavailability of non-haem iron through dietary strategies, such as consumption of ascorbic acid alongside iron-rich foods, may mitigate the inhibitory effects of such compounds as polyphenols, phytates, and other dietary inhibitors [29, 225, 258, 259].

In the context of dietary iron, the distinction between haem and non-haem iron is crucial because of their different absorption mechanisms and efficiencies. Haem iron, found mainly in animal products, is absorbed more efficiently than non-haem iron, although the exact mechanism of its uptake by intestinal enterocytes is not well understood [242]. Non-haem iron found in plant foods is transported across the apical membrane of intestinal enterocytes by divalent metal ion transporter 1 (DMT1) and exported into the bloodstream via ferroportin 1 (FPN1) [259]. Once in the bloodstream, newly absorbed iron binds to plasma transferrin and is distributed to various sites in the body, particularly the erythroid bone marrow, which has high iron requirements [39]. Transferrin-bound iron binds to transferrin receptor 1 on the surface of most somatic cells and, after endocytosis, iron enters the cytoplasm via DMT1 in the endosomal membrane [39]. The bioavailability of dietary iron also depends on the balance between the inhibitors and enhancers of iron absorption [64]. Dietary components affect iron availability through chemical reactions in the stomach and small intestine lumen, as shown in Fig. 9.

The amount of iron absorbed from a food or meal by an individual is determined by physiological variables, such as body iron status, combined with the modulating effects of dietary inhibitors and enhancers. The major dietary enhancers of iron absorption include vitamin C (ascorbic acid), meat, poultry, fish, and alcohol. In contrast, the inhibitors include tannins (found in tea and coffee), calcium and dairy products, polyphenols, phytate, animal proteins (from milk and eggs), and other micronutrients, such as zinc and copper [29, 238].

The analysis and summary of dietary sources of L-ascorbic acid, as reported in various studies [256, 258], highlight its important role in enhancing iron absorption from meals. Ascorbic acid enhances iron absorption by reducing Fe^{3+} to the more soluble Fe^{2+}, which is necessary for transport into mucosal cells [248]. Ascorbic acid also binds iron, preventing it from forming complexes with phytate or tannins that would otherwise make it unavailable to the divalent metal transporter. An increase in iron absorption is directly proportional to the amount of ascorbic acid consumed, within a range of 25-1000 mg [260]. This reducing property of ascorbic acid is one reason why fruit and fruit juices increase dietary iron absorption [234, 255]. Vitamin C has a beneficial effect only when taken with meals [261]. Alcohol has also been positively associated with iron absorption. It increases the permeability of the intestinal mucosa to iron and, through the relatively high iron content in certain wines and beers, contributes to iron absorption [262, 263].

As reported by Briguglio et al. [248], the dietary sources with the highest levels of L-ascorbic acid (vitamin C) vary significantly between fruits and vegetables. Among fruits, raspberries lead with 198 mg of vitamin C per 100 g, followed by kiwi with 141 mg per 100 g, lemons with 129 mg per 100 g, and oranges with 50 mg per 100 g. Among vegetables, peppers are particularly rich in vitamin C with 584 mg per 100 g, followed by cabbage with 348 mg per 100 g and onions and garlic with 183 mg per 100 g [248]. These findings highlight the importance of inclusion of a variety of fruits and vegetables in the diet to ensure adequate vitamin C intake. In particular, raspberries and peppers stand out as remarkable sources, making them excellent choices for increasing daily vitamin C levels. Overall, the diverse range of vitamin C-rich foods highlights the potential of dietary planning to improve the nutritional status and overall health of blood donors.

In contrast to influencers, some inhibitors reduce dietary iron absorption. The main dietary inhibitors of iron absorption are phytic acid, polyphenolic compounds, phosphates, soy protein products, and various dietary fibres [29, 225]. Phytic acid binds to minerals

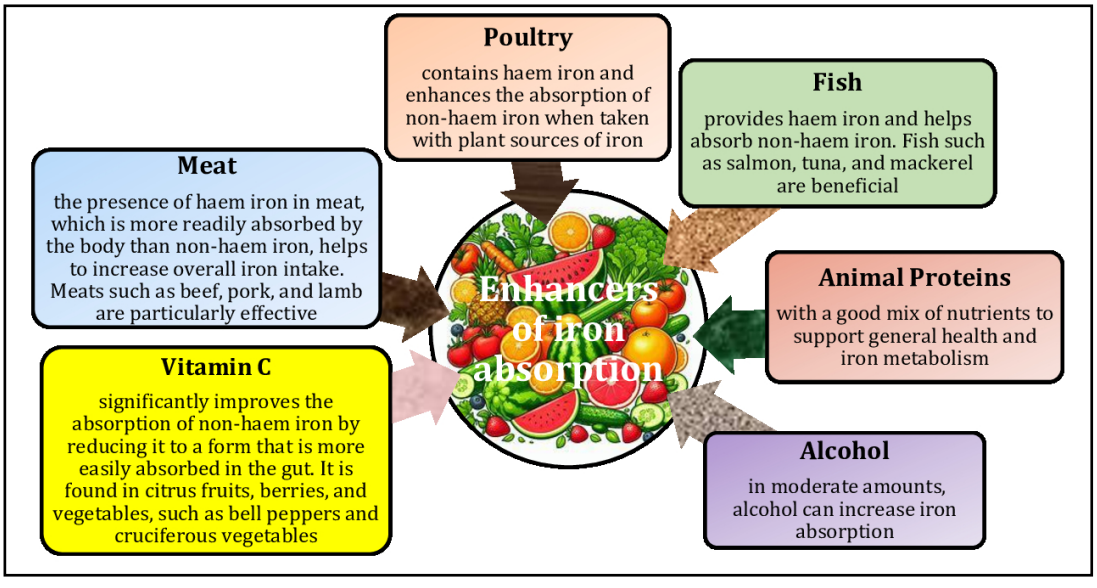

Fig. 9. Enhancers of iron absorption. Understanding factors that influence iron absorption and utilisation is crucial, particularly for those at risk of iron deficiency such as blood donors, pregnant women, and athletes. These factors can be broadly categorised into those that enhance and those that inhibit iron absorption.

and renders them unavailable due to its chelating properties. It is found in particularly high concentrations in cereals (wheat, maize, rice) and legume seeds (beans, lentils, and soya), mainly in the bran of cereals [264]. The content of phytic acid in oilseeds, such as soya beans, sesame seeds, sunflower seeds, linseed, and rapeseed, varies from about 1.0 to 5.4% (dw). Maximum phytic acid content of 10.7% has been reported in soya bean concentrates [265]. Nuts, such as walnuts, almonds, cashews, etc., with phytic acid contents ranging from about 0.1 to 9.4% [266] are another group of phytate-rich foods. The phytic acid content in rice bran was found to be 2.15% [267]. It has been reported that phytic acid inhibits iron absorption. Removal of phytic acid increases the bioavailability of many cations and thus the nutritional value of the meal [265]. Grinding is the most commonly used method to remove phytic acid from cereals but has major drawbacks as it also removes large amounts of minerals and dietary fibre [265]. In addition, soaking cereals such as pearl millet with endogenous or exogenous phytase increases the *in vitro* solubility of iron and zinc by 2-23% [269]. Removal of the bran during wheat and maize flour milling or rice milling can significantly increase iron absorption but results in a significant reduction in the B-group vitamins [270]. Iron absorption from bread made from extra virgin wheat flour is 6 times higher than from whole wheat flour [271].

Many studies have shown that polyphenolic compounds, mainly found in tea, coffee, cocoa, and some fruits and vegetables, inhibit iron absorption [222, 223, 272]. Other dietary inhibitors of iron absorption include calcium from dairy products and certain proteins from milk and legumes [273]. Iron absorption is reduced by foods containing tannins, oxalic and phytic acids, polyphenols, and compounds with galloyl groups found in tannic and gallic acids in tea, coffee, and nuts [33, 274, 275]. In addition, manganese, zinc, lead, chromium, and calcium compete for and alter iron absorption [276-278]. However, ascorbic acid from fruits and vegetables and peptides from partially digested muscle tissue from meat, fish, and poultry can enhance iron absorption and offset some of the negative effects of phytic acid and polyphenols when consumed in a mixed diet [225, 279]. Iron absorption inhibitors shown in Fig. 10.

Therefore, consumption of a variety of nutrient-rich foods and understanding factors that enhance or inhibit iron absorption are crucial for maintenance of optimal iron levels in the blood donor's organism. This is particularly important for those with increased iron requirements, i.e. women and adolescents. Balancing enhancers, such as vitamin C, meat, poultry, and fish, with careful management of such inhibitors as tannins, calcium, and phytate, will help to maximise iron absorption and overall health. Further research and dietary planning are needed to refine these strategies and ensure effective iron intake from a variety of food sources.

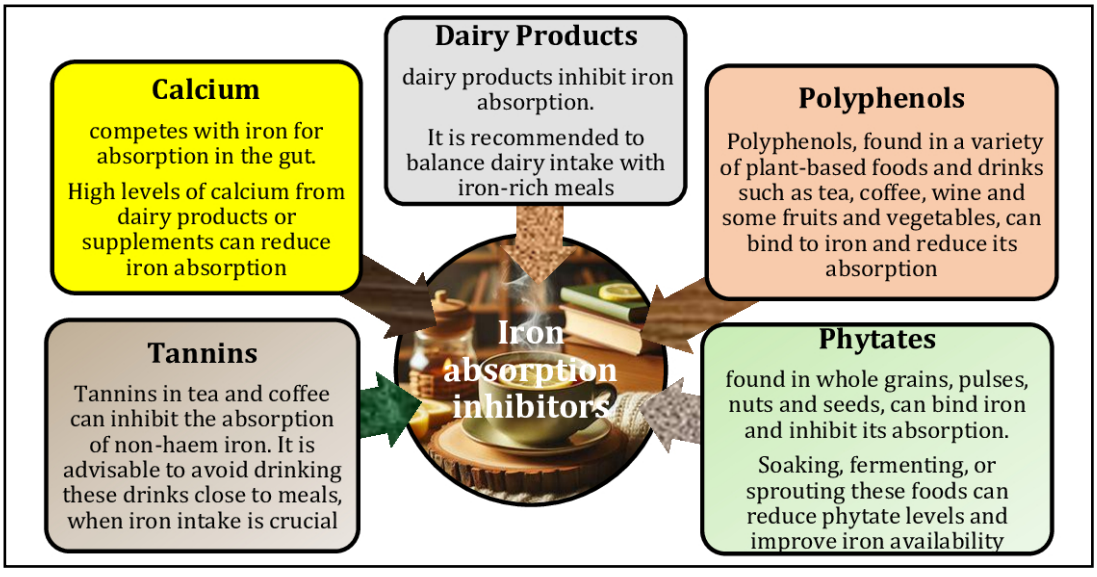

Fig. 10. Iron absorption inhibitors.

Cyancobalamin and folic acid

For blood donors, ensuring adequate intake of both cyancobalamin (vitamin B_{12}) and folic acid (vitamin B_{11}) is critical for maintenance of an optimal red blood cell count [280, 281]. Erythroblasts require folate and vitamin B_{12} for proliferation during differentiation. Folate or vitamin B_{12} deficiency inhibits purine and thymidylate synthesis, impairs DNA synthesis, and leads to erythroblast apoptosis, resulting in anaemia due to ineffective erythropoiesis [282]. The classic clinical manifestation of B_{12} deficiency is macrocytic or megaloblastic anaemia, characterised by enlarged erythrocytes and hypersegmented neutrophils. Megaloblastic anaemia induced by B_{12} deficiency is essentially identical to megaloblastic anaemia caused by folic acid deficiency [283].

Vitamin B_{12} is found in foods of animal origin, including fish, meat (e.g. beef, veal, mutton, and lamb), poultry, eggs, and dairy products (bovine milk and fermented milk, such as yoghurt and cheese) [284]. The best dietary sources of vitamin B_{12} are animal-based foods such as meat, fish, eggs, and dairy products [285, 286]. Raw liver from beef, pork, and chicken is rich in B_{12} (52.8, 25.2, and 44.4 µg/100 g wet weight, respectively). The B_{12} content in raw meat (about 1.0-2.0 µg/100 g wet weight) is higher in beef than in pork (about 0.5 µg/100 g wet weight) or chicken (<0.5 µg/100 g wet weight) [287]. B_{12} concentrations in milk from ruminants, such as sheep (0.71 µg/100 g milk), cow (0.35 µg/100 g milk), and goat (0.06 µg/100 g milk), are higher than in human milk (0.04 µg/100 g milk) [284]. Raw and cooked whole hen eggs contain 0.9 µg of B_{12} per 100 g wet weight of the edible part, with its highest levels in the yolk [288]. Trace amounts (<0.1 µg/100 g dry weight) of B_{12} have been found in dried fruiting bodies of black morels, oyster mushrooms, parasol mushrooms, and porcini mushrooms [289]. Folate is naturally present in many foods, including vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, seafood, eggs, dairy products, meat, poultry, and cereals [290]. Foods with the highest folate content include spinach, liver, asparagus, and Brussels sprouts (Fig. 11).

Vitamin B_{12} plays an important role in the metabolism of methylmalonic acid and homocysteine, which are essential for DNA synthesis [283, 291]. Cobalamin works with folic acid in the methylation cycle required to convert homocysteine to methionine [292]. Methionine is an amino acid used to produce S-adenosylmethionine, a key donor of methyl groups for various methylation reactions, including those involved in DNA and RNA synthesis [291]. Folate, in the form of methylenetetrahydrofolate, is a necessary substrate for the conversion of uridylate to thymidylate and the subsequent incorporation of thymidine into DNA. Folate deficiency inhibits DNA synthesis in blood cell precursors in the bone marrow, preventing mitosis while allowing cytoplasmic maturation. The result is an increased cell volume but a reduced number of circulating red blood cells (i.e. megaloblastic anaemia)

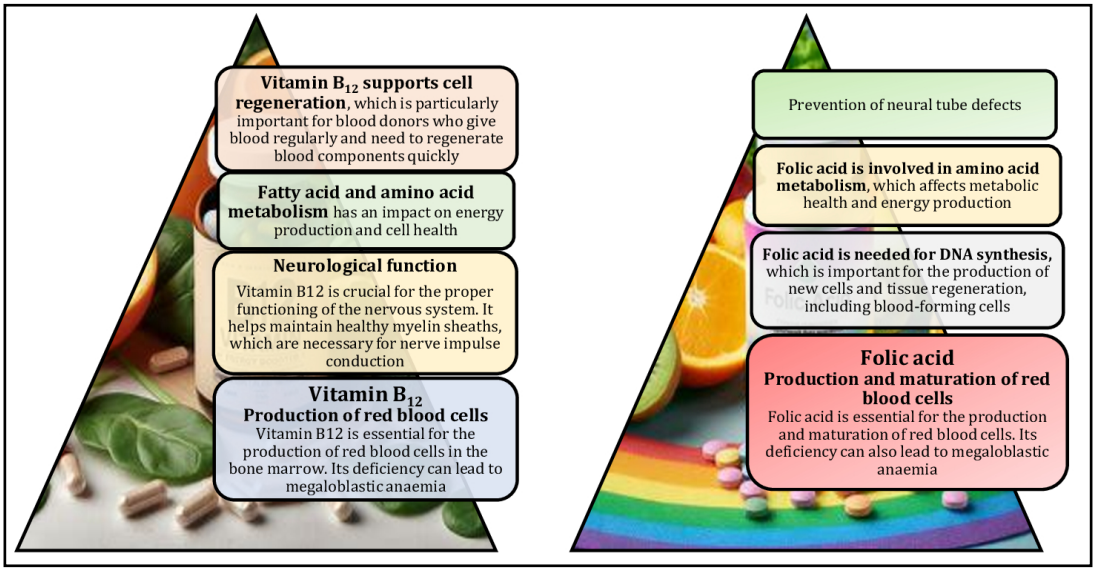

Fig. 11. Vitamin B_{12} and folic acid are essential for the production of blood components and efficient body function, which is particularly important for blood donors who need optimal regeneration after blood loss.

[283]. B_{12} deficiency inhibits the conversion of homocysteine and methyltetrahydrofolate to methionine and tetrahydrofolate. Folate is trapped as methyltetrahydrofolate and therefore cannot serve as a substrate for thymidine synthesis. This results in a functional folate deficiency and megaloblastic anaemia [283]. In addition to megaloblastic anaemia, the other classic pathophysiological manifestation of B_{12} deficiency is neuronal demyelination, which affects both the peripheral and central nervous systems [293] and shown in Figs 9 and 10.

Blood donors on vegetarian or vegan diets may need supplements or fortified foods to meet their vitamin B_{12} needs [285]. Meat, fish, eggs, and dairy products as sources of vitamin B_{12} and plant foods, such as green leafy vegetables (e.g. spinach and kale), legumes (e.g. beans and lentils), and fortified cereals, as sources of folate help to maintain adequate levels of vitamin B_{12} and folic acid to support effective red blood cell production and overall health, which is essential for those who donate blood regularly [284-286, 292].

Vitamins and minerals

Vitamins A, C, and E, together with essential minerals, such as zinc and copper, work synergistically to protect cells from oxidative damage, support immune function, and ensure proper tissue repair [294]. To maintain donor health and promote overall well-being, it is important to ensure adequate intake of these nutrients through a balanced diet or supplements. A diet rich in these vitamins and minerals can help blood donors to maintain optimal health and support effective recovery [295, 296].

For blood donors, vitamins A, C, and E are essential for maintaining health through their roles as antioxidants and regulators of cellular processes, reproduction, embryonic development, and growth [160]. Vitamin A (retinol) is essential for maintaining healthy vision, immune function, and cellular differentiation [297]. At the molecular level, vitamin A has an impact on gene expression by activating nuclear receptors, such as retinoic acid receptors, which regulate the transcription of genes involved in cell growth and immune responses [298, 299]. This modulation helps to maintain the integrity of epithelial tissues and supports immune cell function, which is critical for donors to recover effectively after blood donation [297]. The recommended dietary allowance (RDA) for men and women is 900 and 700 μg retinol activity equivalents (RAE)/day, respectively. The tolerable upper intake (UL) for adults is set at 3, 000 μg/day of preformed vitamin A. The median intake of vitamin A ranges from 744 to 811 μg RAE/day for men and from 530 to 716 μg RAE/day for women [300]. The main dietary sources of provitamin A are foods of animal origin, especially liver, meat, milk, dairy products, and fish. On the other hand, provitamin A carotenoids are found naturally mainly in yellow, red, and orange fruits and vegetables, such as carrots, sweet potatoes, squash, and broccoli [301]. The highest levels of retinol (18000-500 μg/100 g) are found in cod liver oil, liver, eel, butter, chicken eggs, pecorino cheese, and caviar. The highest levels of provitamin A carotenoids (36000-3000 μg/100 g) are found in paprika, parsley, carrots, basil, sweet potatoes, cabbage, red peppers, yellow squash, mango, and radicchio [248].

Vitamin C (ascorbic acid) is a potent water-soluble antioxidant that protects cellular components from free radicals generated during metabolism and has anti-atherogenic, anti-carcinogenic, and immunomodulatory effects [302]. In addition, ascorbic acid is a cofactor for several enzymes, such as dopamine B-monooxygenase or prolyl 4-hydroxylase and lysyl hydroxylase [303]. It plays a crucial role in the synthesis of collagen, carnitine, and neurotransmitter biosynthesis [304]. Collagen synthesis is essential for the structural integrity of blood vessels and skin [305]. Vitamin C works synergistically with vitamin E to quench free radicals and regenerate reduced vitamin E [160]. Natural sources of vitamin C include sour fruits, green vegetables, and tomatoes. Good food sources include red and green peppers, kiwi fruit, broccoli, strawberries, Brussels sprouts, and cantaloupe [306]. Ascorbic acid can be lost during cooking, as it is a labile molecule [302]. Vitamin C also enhances the absorption of non-haem iron from plant foods [99]. This is important for replenishing iron stores after blood donation.

Vitamin E (tocopherol) is a fat-soluble antioxidant protecting cell membranes from oxidative damage by neutralising lipid peroxyl radicals [307]. It also protects polyunsaturated fatty acids in membrane phospholipids and plasma lipoproteins through its peroxyl radical scavenging activity [308, 309]. Vitamin E supplements can reduce measures of lipid peroxidation in subjects with oxidative stress, for example by reducing urinary F2-isoprostanes in hypercholesterolaemic subjects [310] and in diabetics [311]. Vitamin E has been shown to stimulate the body's defences, improve humoral and cellular immune responses, and enhance phagocytic functions. It has a pronounced effect in infectious diseases involving immune phagocytosis, but is less effective in cell-mediated immune defence [307]. Vitamin E is found in a variety of foods, including nuts, seeds, and vegetable oils. It is also found in green leafy vegetables and fortified cereals [307]. Vitamin E works with vitamin C to prevent oxidative damage and support immune function, helping to stabilise cell membranes and reduce inflammation [160], which is important for maintaining the overall health of donors. By reducing oxidative stress, vitamin E supports the recovery of red blood cells and other tissues affected by blood donation.

Minerals, such as zinc and copper, are essential trace elements playing an important role in maintaining donor health. Zinc is considered essential for erythropoiesis, along with iron, folate, and vitamin B_{12} [312]. It is the second most abundant metal in humans, with a total of 2-3 g, and is unevenly distributed in different organs and tissues [313]. Zinc has an impact on many aspects of the immune system, DNA synthesis, and cell division [314, 315]. It plays a crucial role in cell proliferation, differentiation, and apoptosis. Intermediate metabolism, DNA synthesis, reproduction, vision, taste, and cognition all depend on zinc [316]. Zinc is essential for the normal development and function of cells that mediate innate immunity, neutrophils, macrophages, and NK cells. Phagocytosis, intracellular killing, T and B cell function, and cytokine production are all affected by zinc deficiency [315]. Its ability to act as an antioxidant and stabilise membranes suggests a role in preventing free radical-induced damage during inflammatory processes [316]. Zinc retards oxidative processes in the long term by inducing the expression of metallothioneins. These metal-binding cysteine-rich proteins are responsible for maintaining zinc-related cellular homeostasis and act as potent electrophilic scavengers and cytoprotectors [316]. The current recommended dietary allowance (RDA) for zinc proposed by the Institute of Medicine is 11 mg/day for men and 8 mg/day for women [251]. Red meat and oysters are rich dietary sources of zinc [313]. Adequate zinc levels are necessary for proper immune response and wound healing, which is particularly important for donors recovering from blood donation.

Copper is another essential mineral that plays a critical role in physiological processes, such as respiration, connective tissue formation, wound repair, macronutrient energy metabolism, catecholamine biosynthesis, and iron flux [317]. Copper is a redox-active metal ion serving as a catalytic and structural co-factor for enzymes involved in energy production, iron uptake, oxygen transport, cellular metabolism, maturation of peptide hormones, blood clotting, signal transduction, and a host of other processes [318]. Copper is also involved in the formation of collagen and elastin [319], which are important for maintaining healthy blood vessels and tissues. The Recommended Dietary Allowance (RDA) is 0.9 mg/day for adults. The average daily intake of Cu is estimated to be between 1.0 and 1.6 mg/day, well above the RDA [320]. The most common foods containing Cu are shellfish, meat, seeds, nuts, lentils, green leafy vegetables, and cocoa [321].

Role of a healthy lifestyle in blood donation

The 'healthy donor effect' refers to a bias in health research involving blood donors, where donors tend to be healthier than the general population [322]. This phenomenon occurs because individuals who donate blood are usually required to meet certain health criteria, making them a self-selected group of relatively healthy individuals. As a result, studies of blood donors may not accurately reflect the health status of the wider population,

leading to potential methodological problems in research findings. The healthy donor effect, analysed in study [53], is therefore a major methodological challenge in the blood donor health research. By studying its various components, researchers can better understand and manage this bias, achieving more accurate and reliable results [140]. Recognising and correcting for the healthy donor effect is essential to advance the knowledge of the health impact of blood donation and to improve the safety and effectiveness of blood transfusion services [323].

In addition to diet and exercise, proper hydration and sufficient sleep are essential to a healthy lifestyle when donating blood. Hydration is particularly important because blood is mostly water, and adequate fluid intake helps to maintain blood volume and pressure, making the donation process smoother and reducing the risk of dizziness or fainting [324]. Sleep, on the other hand, allows the body to repair and regenerate, which is critical for blood cell recovery and overall energy levels [325, 326]. By prioritising these aspects of a healthy lifestyle, blood donors can ensure that they are in the best possible condition to donate, ultimately contributing to the effectiveness and sustainability of blood donation programmes [327].

Blood donation is known to result in a loss of iron per donation [14] and shown in Figs 2 and 4. Regular physical activity helps to optimise iron absorption and mobilisation, thereby reducing the risk of iron deficiency and associated anaemia, which may affect the donor's ability to continue donating [328, 329] and shown in Fig. 8. Exercise training is known to reduce the circulating ferritin concentration as a biomarker of whole-body iron stores in healthy adults [330, 331]. This is due, at least in part, to increased iron consumption as a result of increased erythropoiesis, which is known to occur with endurance training [329]. Increased erythropoiesis and iron turnover, especially in men [75, 76, 78] compared to women, with regular exercise supports faster recovery of haemoglobin and red blood cell levels after donation. This allows donors to return to their pre-donation health status more quickly, ensuring that they can donate more frequently without adverse effects.

A study by Ziegler et al. [332] showed that individual recovery was variable, but physical performance was recovered 14 days after a standard blood donation, despite the blood haemoglobin concentration remaining lower than at baseline. In another study, blood donation caused a significant decrease in VO_2peak for 2-3 weeks. The practical application of this study is that aerobic performance is reduced for up to 3 weeks after blood donation in people of average fitness. However, in an incremental test on a cycle ergometer, there was no effect of blood donation on performance measured by time to fatigue [333]. Therefore, the role of a healthy lifestyle in blood donation is paramount to ensure the well-being of donors and the quality of donated blood.

Regular physical activity and iron metabolism

Physical activity is an important aspect of a healthy lifestyle that benefits blood donation [334]. Regular exercise improves cardiovascular health and circulation and helps to maintain a healthy weight, all of which contribute to a donor's overall fitness [335]. Exercise also stimulates the production of red blood cells, which contributes to faster recovery after donation. However, it is important for donors to balance their physical activity with adequate rest and nutrition, as intense exercise without proper recovery can deplete the body's resources, including iron and other vital nutrients, making recovery after blood donation more difficult [327].

Regular physical activity affects iron metabolism through a number of mechanisms, including enhanced erythropoiesis, increased iron turnover, and improved iron absorption [336]. It is known that regular physical activity stimulates erythropoiesis – the production of red blood cells – to meet the increased oxygen demand of active muscles [337]. This increased erythropoietic activity lowers hepcidin levels, which increases iron absorption and mobilisation from body stores to support red blood cell synthesis [338]. It is important

to note that physical activity increases red blood cell turnover, which requires efficient recycling of iron from senescent (old) cells. Macrophages in the spleen and liver break down these cells, releasing iron, which is then transported by transferrin to the bone marrow for the production of new red blood cells [339]. Another mechanism is that regular exercise improves the efficiency of intestinal iron absorption, probably by modulating hepcidin levels and upregulating iron transport proteins, such as DMT1 and ferroportin [340, 341].

In summary, the molecular mechanisms of iron metabolism are closely linked to regular physical activity, which plays a critical role in maintaining iron balance and supporting donor health [342, 343]. Understanding and harnessing this relationship can help to optimise donor health and ensure a consistent and reliable supply of high quality blood to those in need. For example, a nutritious diet rich in essential vitamins and minerals is vital for the production of high-quality red blood cells and effective post-donation recovery [296], and regular physical activity improves iron metabolism and general health, facilitating faster recovery and supporting long-term donor health [344]. In addition, maintenance of psycho-emotional well-being through proper nutrition improves mental health, reduces stress, and enriches the donation experience [86].

Psycho-emotional responses and their relationship with diet

The role of a healthy lifestyle in blood donation is also crucial, and it is important that individuals who donate blood regularly maintain a healthy lifestyle [345], as this has a direct impact on both the quality of the blood donated and the donor's recovery process. The modern diet, often characterised by processed foods and nutrient imbalances, may not meet the specific nutritional needs of blood donors [346]. Therefore, comparing the typical modern diet with the nutritional requirements of blood donors highlights key differences and areas for improvement specific to the donor population. Understanding these differences provides insights into how dietary adjustments can improve the health and performance of blood donors – something that is important not only for donors but also for a wide group of people interested in a healthy lifestyle (Fig. 1).

The process of donating blood can elicit various psycho-emotional responses in donors, ranging from anxiety and stress to feelings of altruism and satisfaction [347]. These responses are controlled by complex molecular mechanisms involving the brain, neurotransmitters, and hormones. In addition, diet can play an important role in modulating these psycho-emotional states, thereby influencing the overall donation experience and the donor recovery process. By supporting mental and emotional well-being throughout the donation process, nutrition plays an important role in modulating these responses. Understanding and harnessing these relationships can help donors to improve their donation experience and recovery, ultimately contributing to the sustainability of blood donation programmes [41, 68, 101].

A healthy lifestyle includes regular and varied physical activity, a balanced diet rich in fresh fruit and vegetables, adequate sleep, and healthy habits, such as avoidance of smoking and excessive alcohol consumption [344, 345]. It also includes mental health through stress management techniques, social interactions, and positive relationships, all of which contribute to the overall well-being and quality of life [348]. Maintaining these elements helps to promote physical fitness, emotional resilience, and a positive outlook on life. A balanced diet rich in essential nutrients, regular physical activity, adequate hydration, and sufficient sleep all contribute to the overall well-being of the donor and the efficiency of the blood donation process. A healthy lifestyle ensures that donors have optimal levels of haemoglobin, iron, and other key components that are essential for the production of high quality blood and the rapid regeneration of blood cells after donation [101].

The main mechanisms of psycho-emotional responses associated with blood donation include the state of mind, hormonal responses, stress-reducing nutrients, hydration, electrolyte balance, and antioxidant-rich foods [349] and demonstrated in Fig. 8. Firstly, serotonin plays a crucial role as a neurotransmitter, often referred to as the 'feel good' neurotransmitter, which regulates mood, reduces anxiety, and promotes emotional well-

being [350]. The synthesis of serotonin is dependent on the availability of its precursor, tryptophan, an essential amino acid derived from the diet [351]. Dopamine metabolism is associated with feelings of reward and pleasure. Positive emotions associated with altruistic acts, such as blood donation, can increase dopamine levels [352], thereby increasing the donor's sense of satisfaction and well-being [41]. Some authors highlight the role of cortisol, known as the 'stress hormone', which is released by the adrenal glands in response to stress [353, 354]; elevated cortisol levels can cause anxiety and discomfort. Effective stress management through lifestyle and dietary choices is critical to maintaining balanced cortisol levels [355], especially in blood donors. In recent decades, studies have analysed the multifaceted role of oxytocin, often referred to as the 'love hormone', which is associated with social bonding and positive emotional states [356, 357]. The act of donating blood can stimulate the release of oxytocin, which promotes feelings of connection and altruism [358]. The endocannabinoid system also plays an important role in regulating mood, stress responses, and pain perception [359]. Diets rich in omega-3 fatty acids support the function of the endocannabinoid system [360], potentially helping to modulate stress and anxiety levels in blood donors.

Thus, data from the literature show that fluctuations in serotonin, cortisol and oxytocin levels in blood donors are closely linked to both physiological and psychological responses during and after blood donation [350]. Elevated cortisol levels, particularly in unhealthy donors, indicate increased stress and anxiety, reflecting the body's response to the perceived challenge of donating [353, 354]. Conversely, decreased serotonin levels during the process indicate mood instability and stress, contributing to discomfort. On the other hand, the altruistic nature of blood donation, which promotes social bonding and stress reduction, has been shown to increase oxytocin levels in healthy donors, indicating a positive emotional response [356, 357]. These findings from the literature show how these psychosocial parameters interact and contribute to the variability in donor response.

Some studies have focused on the link between diet and nutritional support for good mood, particularly through tryptophan-rich foods that support serotonin production [361, 362]. Such foods as turkey, eggs, nuts, and seeds are high in tryptophan; it is important for maintaining adequate levels of serotonin, which can help to reduce anxiety and improve mood, thereby enhancing the blood donation experience [351]. Another important amino acid is tyrosine, which is found in chicken, cheese, and soy products. Tyrosine acts as a precursor of dopamine and contributes to feelings of reward and satisfaction after donation when included in a diet rich in tyrosine-rich foods [350]. The stress-reducing nutrients include omega-3 fatty acids found in fish, flaxseed, and walnuts, which reduce inflammation and cortisol levels, improving emotional resilience in donors [363]. In addition, magnesium, found in leafy greens, nuts, and whole grains, supports the regulation of the HPA axis, which is critical for managing cortisol release and mitigating stress responses [364].

Thus, understanding the impact of diet on psycho-emotional health underscores the importance of comprehensive dietary strategies tailored to blood donors. By promoting a nutrient-rich diet, donors can better cope with the emotional and psychological demands of regular blood donation. This approach not only supports their immediate recovery, but also contributes to their long-term mental and emotional well-being. Recognising and addressing the psycho-emotional needs of donors through targeted nutritional interventions can improve the overall donation experience and ensure that donors remain healthy, motivated, and able to consistently provide high quality blood donations.

Practical implications for blood donors emphasise the importance of maintaining a nutrient-rich diet tailored to individual needs, particularly the risk of iron deficiency, which is common among frequent donors. Donors should prioritise iron-rich foods such as lean meats, green leafy vegetables and fortified cereals, complemented by vitamin C sources to enhance iron absorption. Gender-specific dietary recommendations are also critical, as women are more susceptible to iron depletion due to menstruation, requiring additional attention to iron intake. Donors should be educated about the importance of hydration, adequate protein intake, and supplementation with essential vitamins and minerals before and after donation to support recovery and overall well-being. These guidelines aim to promote safe and sustainable donation practices while ensuring the health of the donor.

Conclusion

Based on a systematic search of PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library and ScienceDirect databases, the article provides a comprehensive review of how diet affects the health and performance of blood donors, explains the underlying molecular mechanisms, and offers practical recommendations to support donor well-being and the effectiveness of blood donation programmes worldwide. This article highlights the fact that the diet of blood donors is influenced by gender, as men and women have different nutritional needs and physiological responses, particularly with regard to iron levels and recovery. This highlights the importance of taking gender differences into account when developing dietary recommendations to support the well-being of blood donors. The methodology and approach of this review provides valuable evidence for understanding the complex relationship between health, nutrition, and blood quality and highlights the importance of comprehensive care to ensure that donors remain healthy and able to provide high quality blood donations.

This review provides an analysis of the current literature on improving the health and nutrition of blood donors, examining key aspects that affect the quality of donated blood and donor well-being. Understanding these differences is critical for tailoring dietary recommendations and supplements to maintain optimal iron levels in all donors. Effective iron absorption facilitated by key nutrients, such as vitamin C, plays an important role in replenishing iron stores after donation, ensuring faster recovery and long-term donor health. The review presents evidence on the importance of a balanced diet rich in essential nutrients, minerals such as iron, copper, and zinc, as well as vitamin B_{12} and folic acid, which are essential for blood donors and crucial for red blood cell production and overall blood quality.

The effects of regular physical activity on iron metabolism and general health were also discussed, highlighting how it improves recovery after donation and contributes to donor well-being. Regular blood donation can stress the immune system; therefore, it is important to monitor and maintain donors' long-term health through adequate intake of iron and other key nutrients that support immune function. Psycho-emotional well-being is also linked to diet, with good dietary habits improving mental health, reducing stress, and improving the overall donation experience. To maintain optimal health in blood donors, it is important to include a variety of nutrient-rich foods and to understand factors that promote or inhibit iron absorption.

The healthy donor effect, i.e. a bias in health research where blood donors tend to be healthier than the general population, is discussed in this review. This effect highlights the need for tailored health and nutrition strategies to maintain this higher standard of health among donors. This review assesses whether food fortification with iron could be a cost-effective solution to reduce iron deficiency in blood transfusion recipients and ensure sufficient iron levels to maintain their health and blood quality.

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N.K., H.T., M.G. conceived the concept of the review; N.K., H.T. developed the search strategy; N.K., H.T. coordinated data selection, extraction, analysis, and interpretation; N.K., H.T. critically reviewed the manuscript; N.K., H.T. drafted the final manuscript.

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