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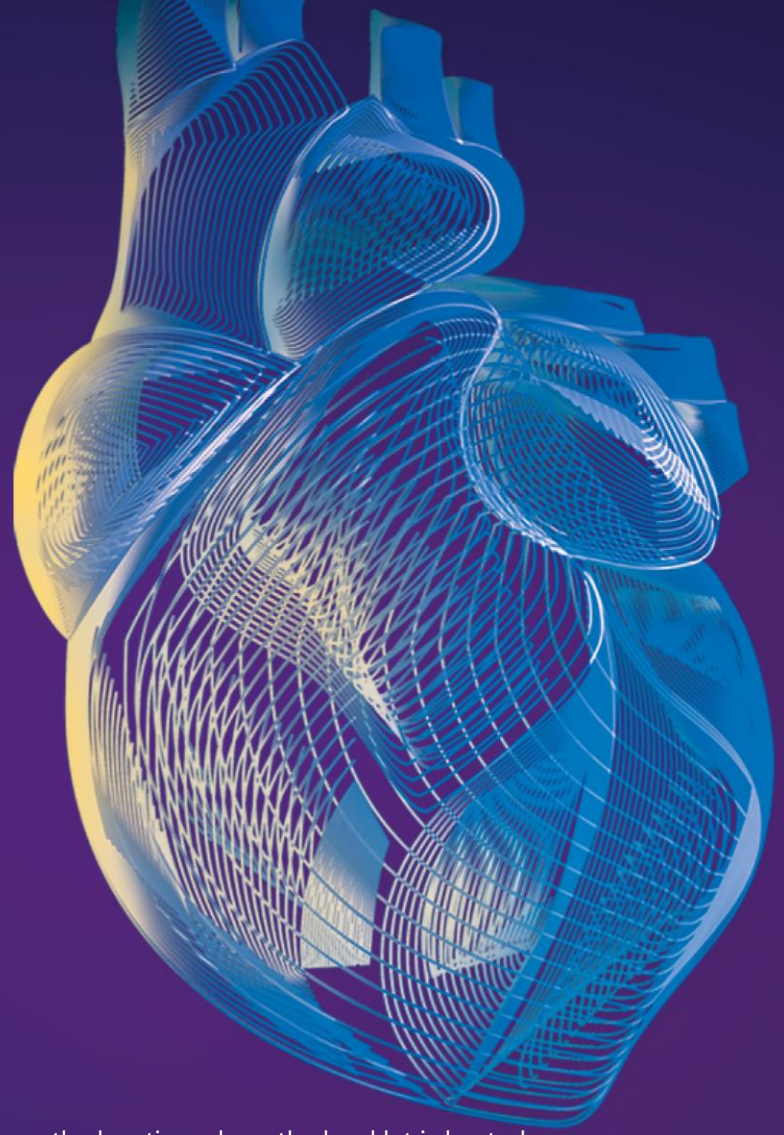
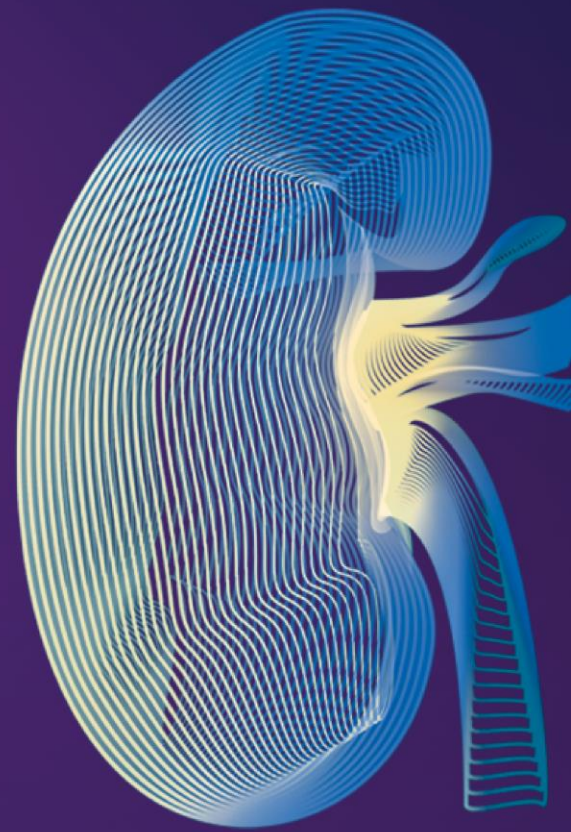
HEART AND KIDNEY IN FOCUS

CLINICAL CASES
IRON DEFICIENCY AND ANAEMIA

INTRODUCTION





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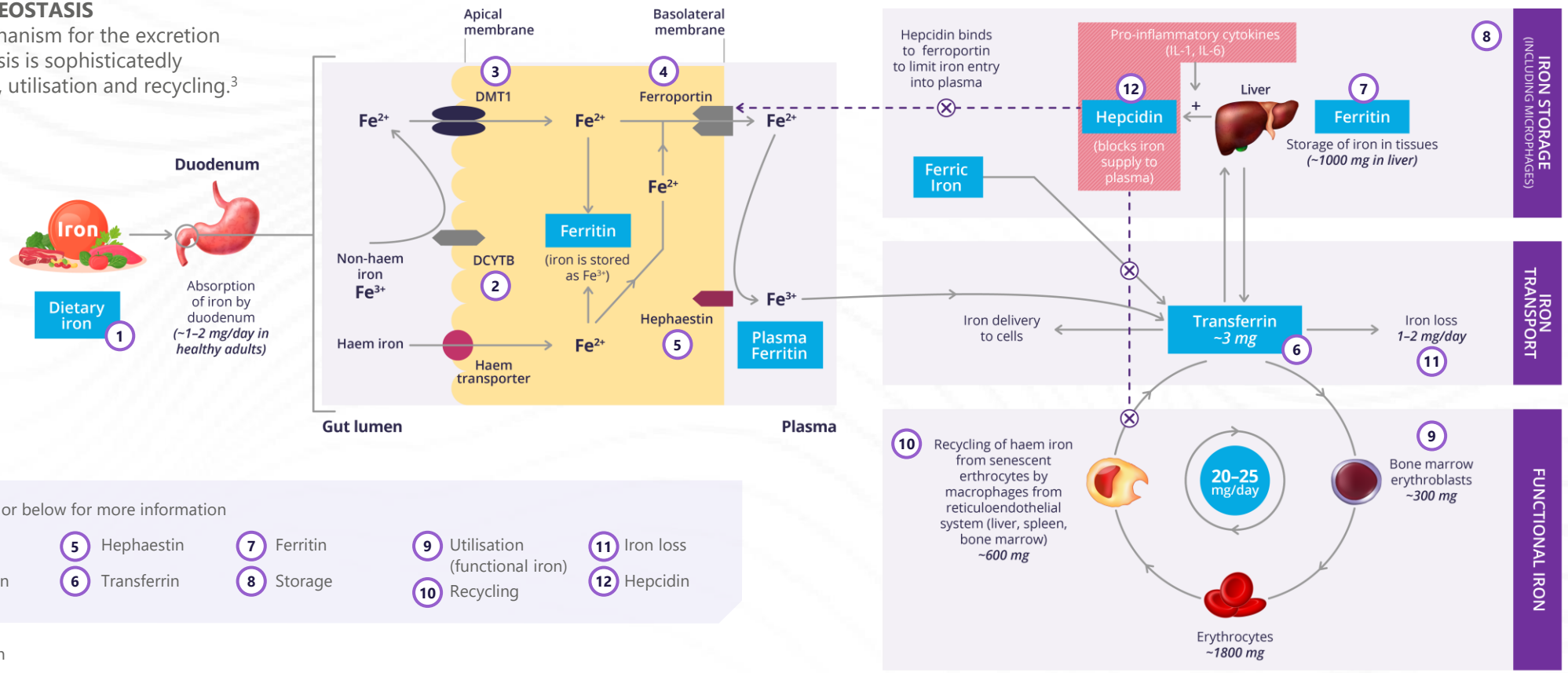
IDA: AN INTRODUCTION

Iron is an essential micronutrient for humans but also extremely toxic in excess, which is why nature has developed a complex system to regulate iron absorption and iron release from stores.[1] Iron is a crucial component of the proteins and enzymes (i.e. haemoglobin [Hb], myoglobin [Mb], cytochromes and peroxidases) needed for almost all essential biological functions, including erythropoiesis, oxygen transport/storage, energy metabolism, antioxidant and pro-oxidant functions and DNA synthesis/repair.[1,2] In a healthy adult, the body contains approximately 3–5 g of iron; approximately 70% is utilised in the erythron, while most of the rest is stored.[1]

THE CIRCLE OF LIFe – IRON HOMEOSTASIS

Since there is no physiological mechanism for the excretion of excess iron, body iron homeostasis is sophisticatedly regulated at the sites of absorption, utilisation and recycling.[3]



KEY Select a number on the diagram or below for more information

1. Dietary iron
2. DCYTB
3. DMT1
4. Ferroportin
5. Hephaestin
6. Transferrin
7. Ferritin
8. Storage
9. Utilisation (functional iron)
10. Recycling
11. Iron loss
12. Hepcidin

Occurs during states of inflammation

REFERENCES

IRON DEFICIENCY IS THE MOST WIDESPREAD NUTRITIONAL DEFICIENCY WORLDWIDE

Iron deficiency is the most prevalent nutritional deficiency worldwide, affecting an estimated 4–6 billion people. It is a standalone medical condition that can be present with or without anaemia,[12,13] although a quarter or more of those with iron deficiency also have anaemia.[13]

The more severe stages of iron deficiency are associated with anaemia, where in the late stages of iron deficiency, the supply of iron to support erythropoiesis is compromised and Hb concentrations are reduced.[14]

Anaemia is defined by low Hb or low red blood cell (RBC) concentration.[14,15]

The World Health Organization (WHO) provides a detailed definition of iron deficiency and anaemia based on ferritin and Hb levels, respectively (see **Table 1**).[15,16]

Table 1. WHO definitions of iron deficiency and anaemia.[15,16]

Iron deficiency[16]	Anaemia[15]
A serum ferritin level of: • <15 µg/L in healthy adults and children aged >5 years • <70 µg/L in adults and children aged >5 years with infection or inflammation • <15 µg/L in pregnant women (first trimester)† Markers of inflammation should be assessed along with the ferritin concentration and ferritin adjusted as necessary.	An Hb level of: • <120 g/L in non-pregnant adult women • <110 g/L in pregnant adult women • <130 g/L in adult men Severe anaemia is defined as Hb <80 g/L in men and non-pregnant women and <70 g/L in pregnancy.

†Physiological changes occurring in pregnancy might contribute to the variation in thresholds of iron deficiency in pregnancy.

Hb, haemoglobin; WHO, World Health Organization.

THERE ARE MULTIPLE CATEGORIES OF IRON DEFICIENCY AND ANAEMIA

Absolute iron deficiency occurs when there are low or absent body iron stores. Causes of absolute iron deficiency include increases in iron requirements, reduced iron intake, or pathological defective absorption or chronic blood loss.[12]

Functional iron deficiency, also known as iron-restricted erythropoiesis, has been defined as the inability to access iron stores to support erythropoietic demands despite adequate iron.[12,17] This may happen as a result of chronic inflammation/infection, or when vigorous erythropoietin causes an imbalance between iron demand and supply.[12]

Iron deficiency anaemia occurs when iron stores are depleted and haemoglobin synthesis is impacted.[17]

Anaemia with functional iron deficiency develops during increased erythropoiesis mediated by either endogenous erythropoietin responses to anaemia, or by therapy with erythropoiesis-stimulating agents, when the iron supply cannot meet the erythron requirements of increased erythropoiesis.[18]

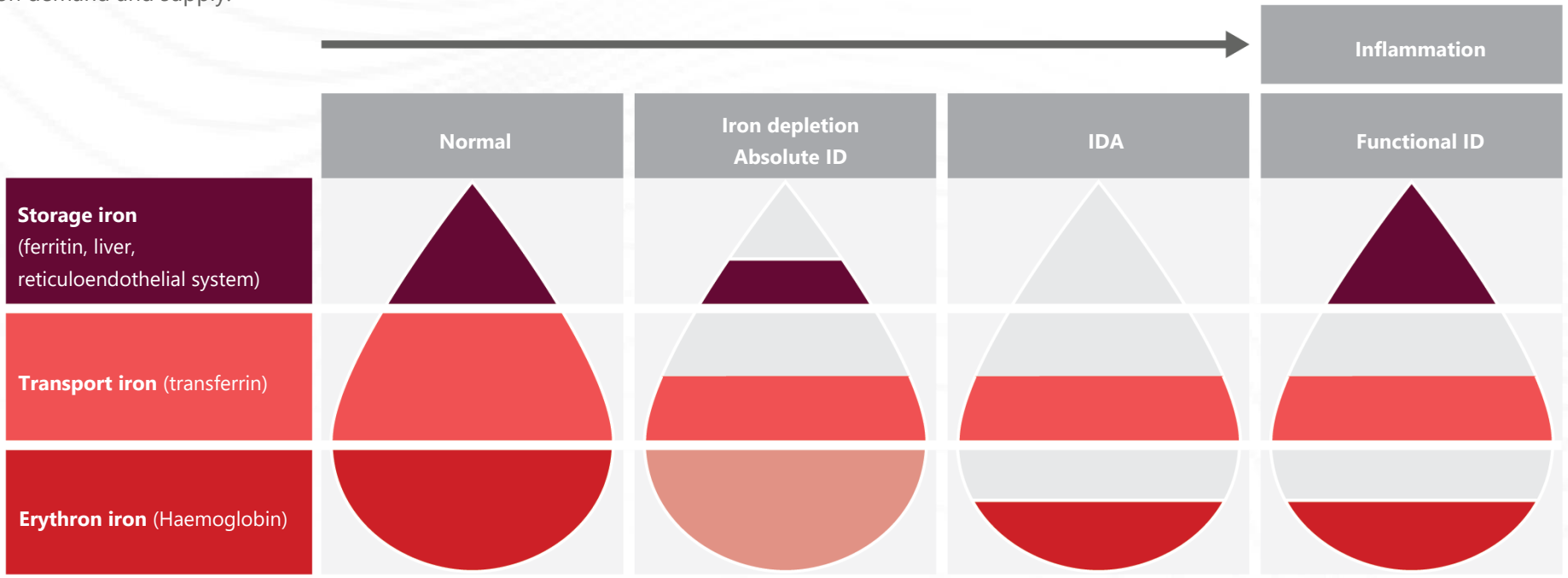


Figure 1. The difference between absolute and functional iron deficiency in relation to body iron stores.
Adapted from Crichton RR et al (2008).[17]

ID, iron deficiency; IDA, iron deficiency anaemia.

HEPCIDIN IS THE MASTER REGULATOR OF IRON IN THE BODY

Hepcidin acts as a central regulator of iron metabolism, controlling absorption and recycling of iron and the volume of iron stores (**Figure 2**).[19]

> Hepcidin maintains iron homeostasis by controlling FPN-mediated delivery of iron from the intestine to circulating transferrin through regulation of FPN expression on cell membranes and the release of iron from macrophages into the circulation.[19]

Hepcidin production in the liver is induced in response to high circulating iron and intracellular iron stores or inflammation (mainly through IL-6 pathways)[1,20]

Suppression of hepcidin is induced by low circulating iron, low ferritin or increased erythropoietic drive[1]

The mechanism of hepcidin upregulation during inflammation or infection[1–3] is likely to have evolved to restrict iron bioavailability in the plasma to pathogens.[3,19]

Click here for information on iron-restricted erythropoiesis >

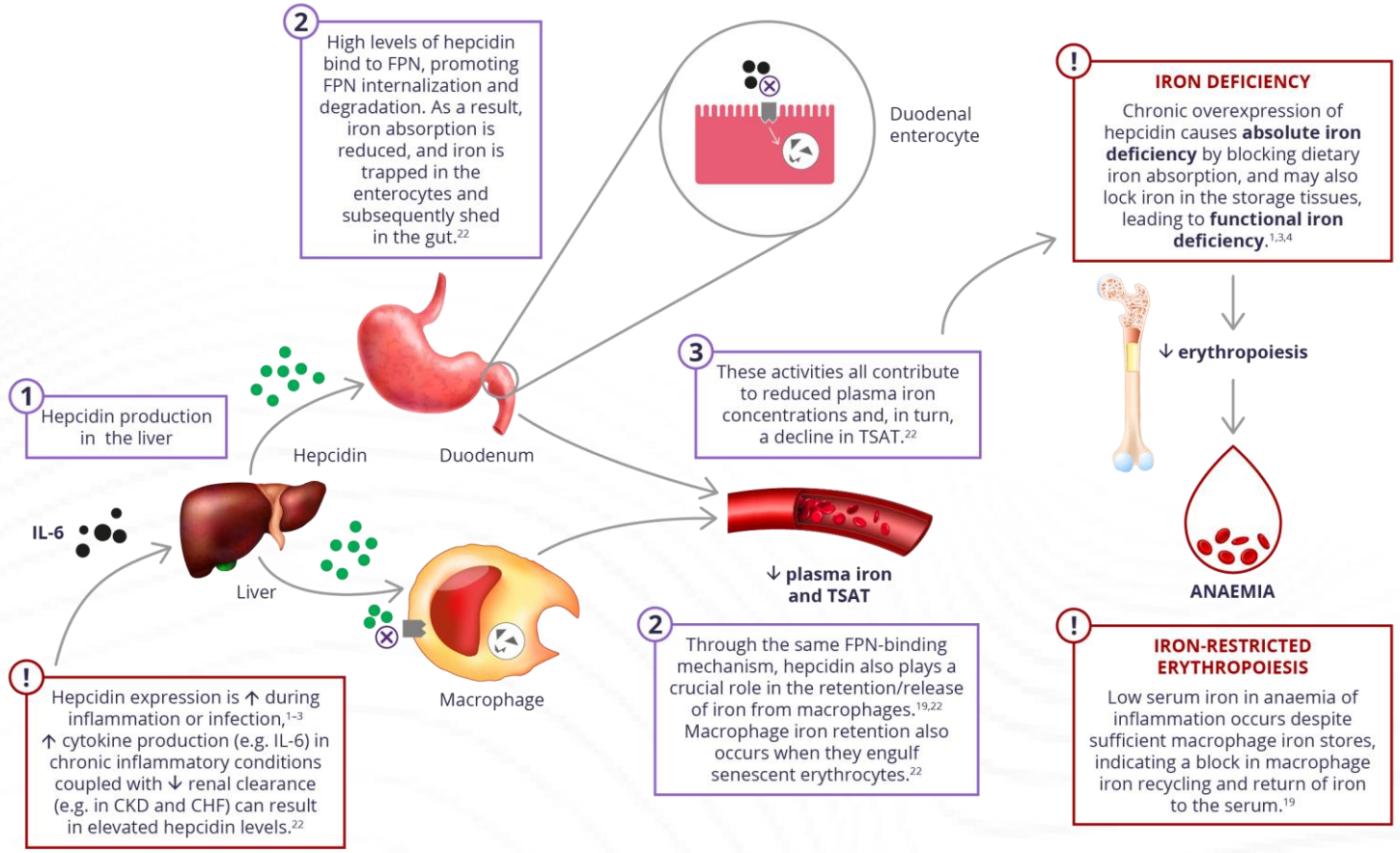


Figure 2. Regulation of iron by hepcidin, and disruption of iron homeostasis during chronic inflammation.

CHF, chronic heart failure; CKD, chronic kidney disease; FPN, ferroportin; ID, iron deficiency; TSAT, transferrin saturation.

BEYOND THE NUMBERS – INTERPRETATION OF LABORATORY TESTS FOR IRON DEFICIENCY AND ANAEMIA

Serum ferritin as a marker of iron status

Under normal physiological conditions, serum ferritin is considered a sensitive marker for iron status. However, many additional factors, including inflammation, infection and malignancy (all of which might elevate serum ferritin levels), complicate the interpretation of this marker.[23]

People with inflammatory conditions might have restricted iron bioavailability due to increased hepcidin expression, despite normal or high levels of serum ferritin. The standard threshold for iron deficiency (ferritin <30 µg/L) therefore does not apply and TSAT should also be assessed.[23] Clinical guidelines in chronic inflammatory diseases such as heart failure and chronic kidney disease (CKD) usually specify both serum ferritin and TSAT thresholds for the diagnosis of iron deficiency, which will be discussed in more detail in the respective chapters.

Appropriate assessment of iron status (including other relevant haematological and biochemistry variables) can help to diagnose iron deficiency and facilitate timely intervention (especially before iron deficiency anaemia develops).[23–26]

Interpretation of laboratory tests to differentiate between iron deficiency and anaemia of chronic disease is summarised in **Table 2**.[17,23,27]

Table 2. Laboratory findings in absolute iron deficiency, functional iron deficiency, IDA and anaemia of chronic disease. Adapted from Crichton et al (2008), Dignass et al (2018) and Schapkaitz et al (2015).[17,23,27]

Laboratory test	Anaemia			Absolute iron deficiency	Functional iron deficiency in inflammation
	ID	CD	ID and CD		
Haematology					
Hb (g/dL)	<12 (F), <13 (M)	<12 (F), <13 (M)	<12 (F), <13 (M)	–	–
MCV	↓	↓ or normal	↓ or normal	–	–
MCH	↓	↓ or normal	↓ or normal	–	–
Retic.Hb (pg)	<28	≥28	<28	↓	↓
Hypochromic red blood cells (%)	>5	<5	>5	↑	↑
Biochemistry					
Serum iron	↓	↓	↓	–	–
TSAT	↓	↓	↓	↓	↓
Ferritin	↓	↑	↓ or normal	↓	↑
CRP	Normal	↑	↑	Normal	↑
Hepcidin	↓	↑	↑	↓	↑

CD, chronic disease; Retic.Hb, reticulocyte haemoglobin content; CRP, C-reactive protein; F, female; Hb, haemoglobin; ID, iron deficiency; M, male; MCH, mean cell haemoglobin; MCV, mean cell volume; TSAT, transferrin saturation.

IRON REPLACEMENT THERAPIES FOR IRON DEFICIENCY

Treatment options for iron deficiency focus primarily on the replacement of iron (iron repletion) with oral supplementation or intravenous (IV) infusion, whereas the therapeutic strategy for anaemia also targets RBCs (transfusion) and erythropoietin (erythropoiesis-stimulating agent [ESA] therapies).[28,29]

Oral iron

For many patients, treatment with oral iron is first-line as it is considered **simple, inexpensive and relatively effective for treating iron deficiency in otherwise healthy people**.[28,30,31]

However, it is well accepted that oral iron effectiveness is often limited by **lack of adherence, intolerance (gastrointestinal side effects), and poor absorption** due to chronic inflammation and consequent upregulation of hepcidin.[30–32]

Table 3. Common oral iron formulations used in the UK and Ireland.[33–35]

Oral iron preparations	Formulation	Elemental iron†
Ferrous sulphate	200 mg	65 mg
Ferrous fumarate	305 mg	100 mg
Ferrous gluconate	300 mg	35 mg

†Total amount of iron available for absorption; different forms of iron supplement provide different proportions of elemental iron.[2]

Providing iron orally in either single daily doses or single alternate-day doses has been shown to optimise iron absorption by minimising an increase in serum hepcidin that can result if doses are given more frequently.[36]

For further information on assessment of therapeutic response to oral iron preparations, click here.

IRON REPLACEMENT THERAPIES FOR IRON DEFICIENCY

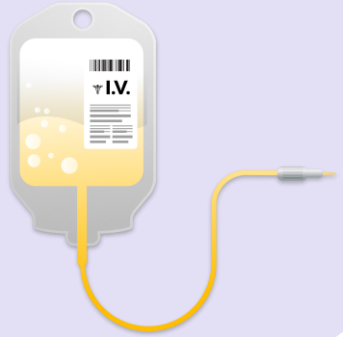
IV iron is administered in the form of iron carbohydrate complexes consisting of polynuclear Fe(III)-oxyhydroxide/oxide core surrounded by a carbohydrate shell. The main function of the ligand is to stabilise the molecule to allow for a controlled delivery of iron to the macrophages of the reticuloendothelial system, where it is then released into the bloodstream.[38]

There are several different parenteral iron products used in clinical practice, for example ferric carboxymaltose (FCM), iron sucrose (IS), ferric derisomaltose (FDI) and iron(III)-hydroxide dextran complex.[30]

Intravenous iron

IV iron is the preferred iron replacement therapy when:[30,37]

- **oral iron preparations are ineffective;**
- **oral iron preparations cannot be used; or**
- **there is a clinical need to deliver iron rapidly.**



The table on the next page (**Table 4**) summarises currently available IV iron formulations.

Differences in iron core size and carbohydrate chemistry determine the pharmacological and biologic differences (e.g. clearance after injection, iron release in vitro, iron bioactivity in vivo, maximum tolerated dose/infusion rate, effects on oxidative markers and immunogenicity) between different iron complexes.[30]

The stability of the different iron formulations correlates with their different physico-chemical characteristics, including molecular weight; complexes with higher molecular weight (e.g. FCM) are generally more stable and contain less labile iron than complexes with lower molecular weight (e.g. IS).[38] The differences in properties of IV iron complexes are reflected in the various approved maximum single doses and administration rates for different products (**Table 4**).

IRON REPLACEMENT THERAPIES FOR IRON DEFICIENCY

Table 4. Selected characteristics of different intravenous iron formulations. Adapted from Munoz et al (2018), Bhandari et al (2018) and Blumenstein et al (2021).[30,39,40]

API	Iron gluconate*	Iron sucrose (Venofer®)	LMWID	Ferric carboxymaltose (Ferinject®)	Ferric derisomaltose	Ferumoxytol*
Carbohydrate[39] (form)[30,40]	Gluconate, loosely associated sucrose (monosaccharide)	Sucrose (disaccharide	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide)	Isomaltoside (linear oligosaccharide)	Polyglucose sorbitol carboxymethylether (polysaccharide)
Molecular weight (Da)[39]	37,500	43,000	103,000	150,000	150,000	185,000
Plasma half-life (h)[39]	Approx 1	6	5–20	7–12	20	Approx 15
Iron content (mg/mL)[30]	12.5	20	50	50	100	30

API, active pharmaceutical ingredient; LMWID, low-molecular-weight iron dextran.

***IV iron formulation not available in Ireland.**

IV IRON TOLERABILITY

IV Iron should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each infusion.[41]

Serious and potentially fatal **anaphylactoid/anaphylactic reactions** are rare with modern IV iron preparations.[38]

High-molecular-weight iron dextran preparations were removed from the market in 2009 because of the risk of serious adverse reactions.[38] Currently available IV iron preparations are associated with a **rare (≥1/10,000 to <1/1000), very rare (<1/10,000) or even lower frequency** of anaphylactoid/anaphylactic reactions.[41–43]

Because of iron's vital role in pathogen reproduction and host immunity, a concern is that IV iron could be associated with **infections**.[19,30] However, current evidence suggests that in the absence of active infection, IV iron replaces iron deficits and does not appear to increase infection risk.[44] It is strongly recommended that IV iron be used with caution in cases of acute or chronic infection and stopped in patients with ongoing bacteraemia.[41]

Hypophosphataemia is a common adverse drug reaction following IV FCM (Ferinject) treatment.[41,45] The mechanism by which FCM infusion drives this response is not fully understood but appears to be related to an increase in circulatory concentrations of biologically active fibroblast growth factor 23 – an osteocyte-derived hormone that regulates phosphate and vitamin D homeostasis, ultimately leading to increased renal excretion of phosphate.[45] Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention, including surgery, has been reported in the post-marketing setting (frequency not known). Patients should be asked to seek medical advice if they experience worsening fatigue with myalgias or bone pain. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.[41]

From here, the prevalence, mechanism, diagnosis, and treatment of iron deficiency and anaemia are discussed in further detail in two sections – 'heart failure' and 'chronic kidney disease' – together with clinical case studies that aim to provide readers with the opportunity to examine and evaluate the unique challenges and overlapping features faced in clinical practice.

ESTIMATING RESPONSE TO ORAL IRON PREPARATIONS

Therapeutic response to oral iron preparations[46]

- Hb concentration should rise by at least 20 g/L (2 g/dL) over 3–4 weeks.
- When Hb is in the normal range, treatment should be continued for a further 3 months to replenish iron stores.

How much iron is needed to increase Hb by 1 g/dL (just accounting for Hb deficit)?[47,48]

- Iron deficit (mg) = (ΔHb g/dL) x bodyweight (kg) x 2.4

$$\textbf{Factor 2.4} = [70\ mL_{blood}/kg_{bodyweight} \times 3.4\ mg_{Fe}/g_{Hb}] / 100\ mL/dL$$

- For someone with 65 $kg_{bodyweight}$ an increase in Hb of 1 g/dL → 156 mg Fe required.

How long will it take to respond to iron therapy in someone with iron deficiency but no inflammation?[49]

- **~17 days** per 1g/dL ΔHb if given as **60 mg iron** (as ferrous sulphate) **dosed every** day (mean fractional iron absorption 16.3%)
- ~**26 days** per 1g/dL ΔHb if given as **60 mg iron** (as ferrous sulphate) **dosed on alternate days** (mean fractional iron absorption 21.8%)

IDA: AN INTRODUCTION – REFERENCES

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Ferinject® (ferric carboxymaltose)

Prescribing Information - Ireland
For full prescribing information refer to the Summary of Product Characteristics (SmPC)
Active Ingredient: Ferric carboxymaltose (50mg/mL)
Presentation: Dispersion for injection/infusion. Available as a 2mL vial (as 100mg of iron), 10mL vial (as 500mg of iron) and 20mL vial (as 1000mg of iron).
Indication: Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used or if there is a clinical need to deliver iron rapidly. The diagnosis must be based on laboratory tests.
Dosage and Administration: The posology of Ferinject follows a stepwise approach:
Step 1: Determination of the iron need:
The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level, using the simplified table in the SmPC. Two doses may be required to replenish the total iron need.
Step 2: Calculation and administration of the maximum individual iron dose(s):
Based on the total iron need determined, the appropriate dose(s) of Ferinject should be administered:
In adults and adolescents aged 14 years and older, the maximum single dose is 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion) and the maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) per week.
In children and adolescents aged 1 to 13 years, the maximum single dose is 15 mg iron/kg body weight, and the maximum recommended cumulative dose of Ferinject is 750 mg of iron (15 mL Ferinject) per week.
In all cases, if the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
Administration rates for intravenous injection using undiluted dispersion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered at a rate of 100mg iron/min. For doses >500mg to 1,000mg, the minimum administration time is 15 min.
Administration of intravenous drip infusion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered in a minimum of 6 mins. For doses >500mg to 1,000mg, the minimum administration time is 15 mins.
Ferinject must only be diluted in 0.9% m/V NaCl but should not be diluted to concentrations less than 2 mg iron/mL.
Step 3: Post-iron repletion assessments
Contraindications: Hypersensitivity to Ferinject or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Ferinject should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention has been reported. Patients should be asked to seek medical advice if they experience symptoms. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. There is no safety data on the use of single doses of more than 200mg iron in haemodialysis-dependent chronic kidney disease patients. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Ferinject is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Ferinject. The efficacy and safety of Ferinject has not been investigated in children below 1 year of age. Ferinject is therefore not recommended for use in children in this age group.
Special Populations: In adults and adolescents aged 14 years and older, a single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients.
In children aged 1 to 13 years with chronic kidney disease requiring haemodialysis, the efficacy and safety of Ferinject has not been investigated. Ferinject is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.
A careful risk/benefit evaluation is required before use during pregnancy. Ferinject should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects: Common (≥1/100 to <1/10): Hypophosphataemia, headache, dizziness, flushing, hypertension, nausea, injection/infusion site reactions. Rare (≥1/10,000 to <1/1,000): Anaphylactic reactions. Frequency not known: Kounis syndrome, hypophosphataemic osteomalacia. Please consult the SmPC in relation to other undesirable effects
Legal category: POM
MA Number: PA0949/004/001
Date of Authorisation: 19.07.2007
MA Holder: Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

Ferinject® is a registered trademark

Document number: IE-FCM-2300011
Date of preparation: 06/2023

Additional information is available on request

Adverse events should be reported. Reporting forms and information can be found at: https://www.hpra.ie
Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633.
Email: MedicalInfo_UK@viforpharma.com

Venofer® (iron sucrose)

Prescribing Information - Ireland
For full prescribing information refer to the Summary of Product Characteristics (SmPC)
Active ingredient: Iron sucrose (20 mg/mL)
Presentation: Solution for injection/infusion. Available as a 5 mL vial (as 100 mg of iron).
Indication: Treatment of iron deficiency where there is a clinical need for a rapid iron supply, in patients who cannot tolerate oral iron therapy or who are non-compliant, in active inflammatory bowel disease where oral iron preparations are ineffective, and in chronic kidney disease when oral iron preparations are less effective. The diagnosis of iron deficiency must be based on appropriate laboratory tests.
Dosage and Administration: The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), must be individually determined for each patient, based on haemoglobin level and body weight and calculated with the Ganzoni formula. The total single dose must not exceed 200 mg of iron given not more than three times per week.
Administration for intravenous drip infusion:
Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution up to a maximum dilution of 1 mg/mL. For iron doses of 50 mg, minimum infusion time is 8 minutes. For doses of 100 mg, minimum infusion time is 15 minutes. For doses of 200 mg, the minimum administration time is 30 min.
Intravenous injection: Venofer may be administered by slow intravenous injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL Venofer (200 mg iron) per injection.
Administration into dialysis machine: Venofer may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.
Contraindications: Hypersensitivity to Venofer or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).
Venofer should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Venofer is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Venofer.
Special populations: The use of Venofer has not been studied in children. A careful risk/benefit evaluation is required before use during pregnancy. Venofer should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects Common (≥1/100 to <1/10): Dysgeusia, hypotension, hypertension, nausea and injection/infusion site reactions. Frequency not known: Anaphylactoid/anaphylactic reactions and Kounis syndrome. Please consult the SmPC in relation to other undesirable effects.
Legal category: POM
MA Number: PA 949/001/002
Date of Authorisation: 11.09.2009
MA Holder: Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

Venofer® is a registered trademark

Document number: IE-VEN-2200001
Date of preparation: May 2022

Additional information is available on request

Adverse events should be reported. Reporting forms and information can be found at http://www.hpra.ie/homepage/about-us/report-an-issue
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Email: medicalinfo_UK@viforpharma.com

IDA: AN INTRODUCTION

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1 **Dietary iron**[1–6]

Iron from food comes in two forms: haem, and non-haem.

After birth, all iron enters the body via diet (excluding exogenous therapeutic sources). **In healthy adults, approximately 2 mg of iron is absorbed** daily in the duodenum and proximal jejunum, but may increase 10-fold in someone who is iron deficient but otherwise healthy.

Haem iron
(~10% of dietary iron)

- Derived from Hb and Mb in meat
- Directly absorbed through a poorly characterised mechanism via the isoforms of haem oxygenase (HO-1/HO-2)
- High bioavailability

Non-haem iron
(~80–90% of dietary iron)

- Predominantly derived from plants (but also found in meat)
- Available as both Fe^{3+} and Fe^{2+} but exists mostly as Fe^{3+}
- Low bioavailability

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2 Ferric reductase duodenal cytochrome B (DCYTB) reduces Fe^{3+} to Fe^{2+} in the duodenal lumen.[1,3]

- Fe^{3+} must be reduced to Fe^{2+} before it can be absorbed, a process that is dependent on the low pH of gastric acid.[1,3]
- This process can also happen with other reductases or non-enzymatic reducing agents such as ascorbate.[1,3]
- The low stomach pH of gastric acid enables DCYTB on the brush border of enterocytes to catalyse the reduction of Fe^{3+} to Fe^{2+}. Increased stomach pH (e.g. due to proton pump inhibitors) may impair reduction to Fe^{2+}.[7]

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3 Divalent metal transporter 1 (DMT1) transports the resulting Fe^{2+} across the apical membrane of enterocytes.[1,3]

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4 **Ferroportin (FPN)** mediates the export of iron (Fe^{2+}) from enterocytes to the blood.[1,3,8]

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5 Conversion of Fe^{2+} to Fe^{3+} occurs at the cell membrane, facilitated by hephaestin or ceruloplasmin, both of which have ferroxidase activity ($Fe^{2+} \rightarrow Fe^{3+}$).[1,3]

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6 Fe^{3+} in the bloodstream is immediately captured by the iron-transport protein, **transferrin (Tf)**.[1,3]
At steady state, plasma Tf contains only 3 mg of iron, but iron turns over ~10 times daily to meet various physiological needs:[1]

- approximately 25–30 mg/day delivered from the plasma to developing erythroid cells in the bone marrow for haem biosynthesis during haemoglobinisation; and
- up to 5 mg/day to other tissues.

Transferrin saturation (TSAT) is a biomarker of iron availability; under normal conditions, more than 30% of the circulating Tf is saturated with iron.[1,9]

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7 **Ferritin** is present in the cytosol of cells, where it binds iron to prevent free-radical damage caused by 'free' iron.[1,3,10]

- Free iron is toxic to cells as it acts as a catalyst in redox reactions that produce free radicals. A small amount of ferritin leaks out from cells and therefore plasma ferritin levels can reflect the size of iron stores.
- Fe^{2+} is oxidised to Fe^{3+} for safe iron storage, mediated by H-ferritin.

In the context of inflammatory disease, cellular ferritin increases in response to inflammation because it is an acute phase reactant, therefore, more ferritin leaks out of cells. **Interpreting serum ferritin in inflammatory conditions is therefore complex**, and thresholds for guiding therapy vary across different clinical situations.[2,3] **High serum ferritin** can also be a marker of severe iron overload.[3]

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8 **Utilisation**[9]

- More than two-thirds of total body iron (>2000 mg) is incorporated into the Hb of the developing erythroid precursors and mature erythrocytes.
- Approximately 300 mg is present in muscles within Mb.
- Approximately 8 mg is present in other cellular iron-containing proteins and enzymes.

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9 **Storage**

Approximately 1 g of total body iron is stored in the **hepatocytes** within ferritin. The **reticuloendothelial system** also serves as a storage depot for excess iron.[9,11]

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10 **Recycling**[3,9]

- **A substantial proportion of body iron** (approximately **600 mg**) is found in a transit iron pool in **reticuloendothelial macrophages**.
  - Reticuloendothelial macrophages are responsible for engulfing senescent erythrocytes through erythrophagocytosis.
  - Inorganic iron is released from haem once the erythrocytes are digested.
  - Iron can be stored in ferritin or returns to the plasma via FPN for reutilisation.

This represents the major source of systemically available iron that can be reused to generate new erythrocytes.[9]

- Additionally, **lysosomes recycle iron** from mitochondria (mitophagy) and cytosolic ferritin (ferritinophagy), respectively, and therefore contain relatively high amounts of intracellular iron at steady state (mostly as Fe^{2+}).[1]

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11 **Iron loss**[3]

The daily iron intake from diet needs to balance the daily iron loss (1–2 mg/day) resulting from the desquamation of skin (skin peeling), sloughing of intestinal epithelial cells and other blood loss (e.g. menstruation).

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12 **Hepcidin** is the central regulator of systemic iron homeostasis.[1–3]

- It is predominantly synthesised in hepatocytes.
- It is the main regulator of plasma iron concentrations.
- **Iron efflux** (i.e. from macrophages, enterocytes) to plasma is **inhibited by binding of hepcidin to FPN**.

HEPCIDIN IS THE MASTER REGULATOR OF IRON IN THE BODY

Hepcidin acts as a central regulator of iron metabolism, controlling absorption and recycling of iron and

> Hepcidin maintains iron h
> FPN-mediated delivery of
> transferrin through regula
> membranes and the relea
> circulation.[19]

Hepcidin production in the
circulating iron and intracellu
(mainly through IL-6 pathway

Suppression of hepcidin is
or increased erythropoietic d

The mechanism of hepcidin u
likely to have evolved to restr
in the plasma to pathogens.[3]

Click here for information

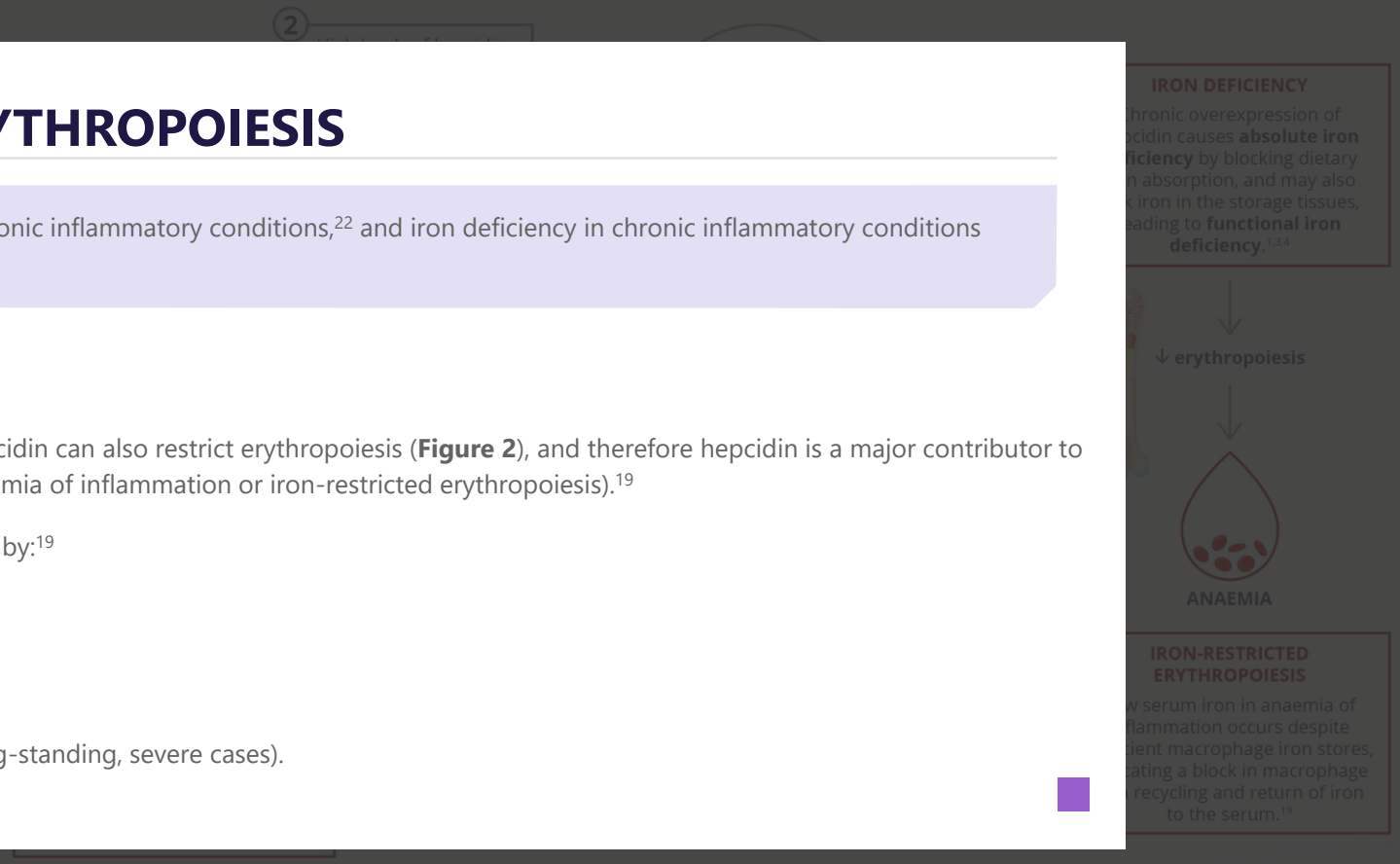

Figure 2. Regulation of iron by hepcidin, and disruption of iron homeostasis during chronic inflammation.
CHF, chronic heart failure; CKD, chronic kidney disease; FPN, ferroportin; ID, iron deficiency; TSAT, transferrin saturation.

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IRON-RESTRICTED ERYTHROPOIESIS

> Iron supply to all organs becomes low in chronic inflammatory conditions,[22] and iron deficiency in chronic inflammatory conditions contributes to disease exacerbation.[22,23]

Iron-restricted erythropoiesis

Limited iron availability caused by elevated hepcidin can also restrict erythropoiesis (**Figure 2**), and therefore hepcidin is a major contributor to anaemia of chronic disease (also known as anaemia of inflammation or iron-restricted erythropoiesis).[19]

Iron-restricted erythropoiesis is characterised by:[19]

- hypoferraemia (low serum iron);
- iron sequestration in macrophages;
- elevated serum ferritin concentrations;
- blunted response to erythropoietin; and
- microcytic and hypochromic red cells (in long-standing, severe cases).