

Iron deficiency before and after bariatric surgery: The need for iron supplementation

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ABSTRACT

Hepcidin inhibits the iron export from duodenal cells and liver cells into the plasma and therefore plays a key role in controlling iron homeostasis. In obese patients, elevated cytokine production stimulates hepcidin synthesis, causing iron to be retained as ferritin in e.g. macrophages (functional iron deficiency). In addition, patients often develop iron deficiency after bariatric surgery due to malabsorption, which may cause anaemia and thereby lead to complaints such as fatigue. In these patients, the absorption of iron may be disrupted because the reduction of Fe³⁺ by gastric acid into Fe²⁺ (the form that is easily absorbed) is not so effective after stomach reduction. Iron absorption is further reduced after malabsorptive interventions as a result of bypassing the duodenum and the proximal part of the small intestine, where the absorption takes place. Oral iron supplements often have little effect after bariatric surgery. Intravenous supplements of iron can restore the iron status rapidly after bariatric surgery, resulting in fewer symptoms such as fatigue.

KEYWORDS

Anaemia, bariatric surgery, hepcidin, intravenous iron supplementation, iron deficiency

INTRODUCTION

Over the past few years, there has been a strong increase in the number of bariatric operations performed, because of the annual increase in the incidence of morbid obesity (BMI >40 kg/m²). In 2011, the Netherlands Association

of Surgeons drew up a new guideline for the treatment of 'morbid obesity'.¹ A review of the role of bariatric surgery in reducing this threat to public health was recently published in this journal.²

The absorption of essential vitamins and minerals is often disrupted after bariatric surgery. The problem of iron deficiency in particular is often underestimated.³ In recent years, new insights have been gained into iron homeostasis and the prevalence, diagnosis and treatment options for iron deficiency related to bariatric procedures. We carried out a literature study in PubMed about this, looking at studies on the subject that have been published over the last five years. This article contains a summary of these studies.

VARIOUS BARIATRIC PROCEDURES

There is a wide range of bariatric procedures and they are generally classified by their assumed mechanism:

- Restrictive procedures: based on limiting the intake of food by gastric reduction, such as sleeve gastrectomy.
- Malabsorptive interventions: based on limiting absorption of nutrients by biliopancreatic diversion (BPD): division of part of the small intestine into two branches, one nutrient branch to transport nutrients and one biliopancreatic branch to transport biliopancreatic juices. This bypass only makes it possible to absorb food via the small remaining common part of the small intestine
- Combined restrictive and malabsorptive interventions, such as a Roux-en-Y gastric bypass (RYGB), combining gastric reduction and biliopancreatic diversion.

More information about these types of bariatric surgery can be found in the previously mentioned review.²

IRON DEFICIENCY ANAEMIA RELATED TO BARIATRIC SURGERY

Prevalence of iron deficiency anaemia before and after bariatric surgery

Anaemia, iron deficiency or a combination of the two often develops after a patient has undergone bariatric surgery. The prevalence figures for anaemia and iron deficiency in 1252 morbidly obese patients before bariatric surgery were 14% and 28% respectively.³ Postoperatively, these percentages were seen to increase to 30-60% for iron deficiency and anaemia, depending on the definition of iron deficiency, the duration of the follow-up period, the type of intervention, the patient population, and supplementation of iron.³ This corresponds to the prevalence figures for anaemia from a large American cohort study (n=1125) of bariatric patients: 12% preoperatively and 23% postoperatively.⁴ Table 1 presents various risk factors for developing iron deficiency and/or iron deficiency anaemia.

Figure 1 shows the results of a Dutch study into the prevalence of anaemia and iron deficiency in 377 patients before and after weight-loss surgery (RYGB).⁵ The percentage of iron deficiency anaemia one year after the operation was 16%. Another 16% of patients showed iron deficiency (without anaemia) and might develop anaemia if no iron supplementation is given.⁵ A drawback of this study is that serum ferritin levels were not measured, the method that has gained widest acceptance as an indicator of iron status.⁶

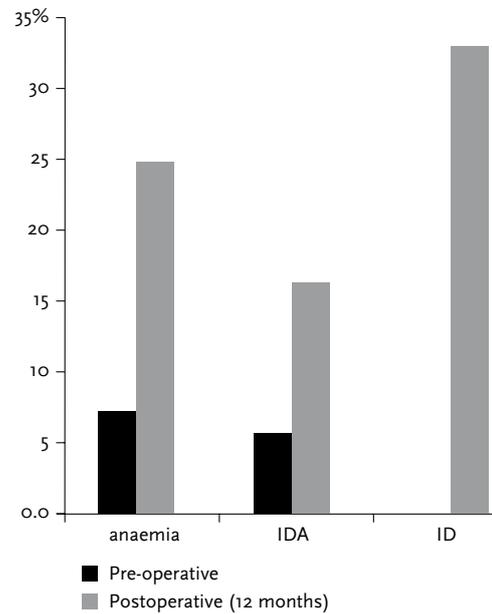
New insights into the regulation of iron status

Iron homeostasis (figure 2) balances out the iron demands of various organs and ensures efficient reuse of iron from macrophages, as well as controlled storage of iron. Most of the iron in our bodies can be found together with

Table 1. Risk groups and risk factors for developing ID and anaemia before and after bariatric surgery

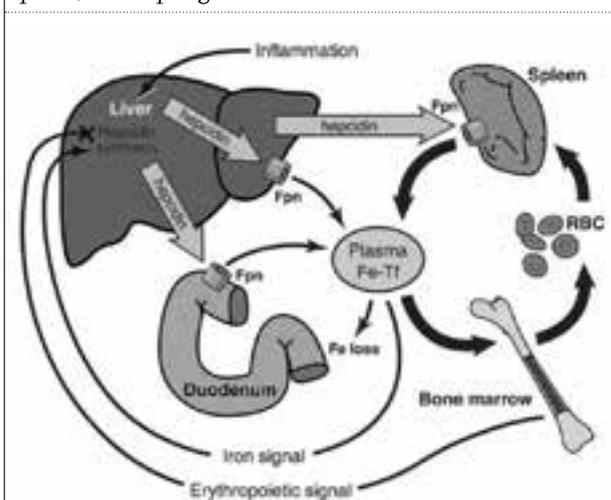
- Women^{5,18} and in particular:
 - premenopausal women^{13,14}
 - pregnant women¹³
- Adolescents^{13,18}
- BMI >50 kg/m²³
- Vitamin B12 deficiency¹⁸
- After malabsorptive interventions (in the long term, the risk is greater than for restrictive interventions)^{3,17}

Figure 1. Prevalence of anaemia*, iron deficiency anaemia (IDA) and iron deficiency* (ID) before and one year after malabsorptive bariatric surgery (RYGB). Figure is based on data from a Dutch study into prevalence of anaemia and related deficiencies (n=377)⁵



* (ID) anaemia = Hb <8.4 mmol/l in men and Hb <7.4 mmol/l in women; ID = serum iron <9.0 µmol/l

Figure 2. Iron homeostasis with hepcidin as the regulator. Storage of iron in red blood cells (RBC), liver, spleen, macrophages and bone marrow⁸



Fpn = ferroportin: release of iron to plasma; Fe-Tf = iron-transferrin complex: transport protein for the iron, RBC = red blood cell.

protoporphyrin in the core of haem, which is used to make haemoglobin in red blood cells and is responsible *inter alia* for oxygen and carbon dioxide transport. When red blood cells are broken down by macrophages, their iron is extracted and stored for reuse.^{7,8}

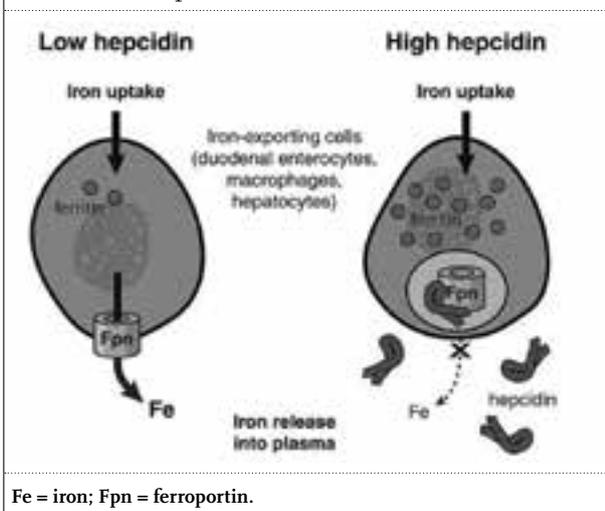
The hormone hepcidin plays a key role in maintaining a balance between iron deficiency on the one hand and accumulation of iron on the other (figures 2 and 3). Hepcidin is produced in the liver and binds to the membrane-bound iron export protein ferroportin, which can be found in duodenal cells, among others. Ferroportin is deactivated after binding: iron can then temporarily not be released into the plasma. The iron is then stored as ferritin in the duodenal cell and the absorption of iron from within the intestinal lumen is inhibited.⁹ If hepcidin production is low, the iron stored will be released to the plasma as needed and transported in the form of transferrin-bound iron to the cells that need iron. Increased erythropoiesis or reduced iron plasma levels inhibit the production of hepcidin, which increases iron release to the plasma. Accumulation of iron and inflammatory processes stimulate the synthesis of hepcidin, thus inhibiting the release of iron to the plasma. As a result, iron remains locked in the duodenal cells and will largely be lost in the faeces after the intestinal cell itself is lost.⁷⁻⁹

Causes and consequences of iron deficiency/iron deficiency anaemia

Causes of iron deficiency and iron deficiency anaemia

Iron deficiency can develop if iron metabolism is disturbed. Causes of such a disturbance include haemorrhage, insufficient iron absorption from the food in the duodenum or increased hepcidin concentrations caused by, for example, inflammation.

Figure 3. *Hepcidin as the regulator of cellular iron release into the plasma*⁸



Over recent years, more insights have been gained into the relationship between obesity and iron levels. Cytokines such as interleukin-6 and TNF- α are produced in fatty tissues, inducing an inflammatory response. Activation of the immune system then results in increased hepcidin production, followed by reduction of iron levels in the plasma and an increase in ferritin (functional iron deficiency). As a result, the production of haemoglobin will be disturbed and anaemia develops.^{3,4,9-11} In addition to their nutritional patterns, this explains the relatively high percentages of iron deficiency and iron deficiency anaemia in patients with morbid obesity prior to bariatric surgery.^{3,5,10,12}

Bariatric surgery often results in drastic weight loss.² In some studies, this weight loss was associated with reduction in the inflammatory status, with recovery from the functional iron deficiency as a result.^{10,12} However, iron deficiency and/or anaemia are observed in most studies in the follow-up period after the bariatric procedure (see above). These mostly referred to malabsorptive interventions. In addition to gastrointestinal blood loss, iron absorption can also be disturbed for various other reasons. As a result of the stomach reduction, non-haem bound Fe³⁺ cannot be reduced effectively by gastric acid to the more easily absorbed Fe²⁺.^{5,13} The uptake of haem iron is disrupted too. The bypass delays the interaction with biliopancreatic juices. It is then more difficult for haem to be released from myoglobin and haemoglobin.¹³ In addition, eating red meat (the major source of haem iron) is less well tolerated after stomach reduction.^{5,13} Finally, iron is mainly absorbed in the duodenum and proximal jejunum.⁷ This absorption cannot take place because this part of the small intestine has been bypassed.^{3,5,13} The length of the remaining part of the jejunum, now used as a branch for transporting food, hardly affects the iron absorption. This suggests that there is no up-regulation of iron absorption further along the small intestine, which could have compensated for the duodenal bypass.¹³ However, this type of up-regulation does occur for some other nutrients, such as folate.^{3,5}

Consequences of iron deficiency and iron deficiency anaemia

Iron deficiency inhibits the synthesis of haemoglobin and may thereby cause anaemia. This often causes severe fatigue,^{3,14} which is undesirable for patients for whom a healthy lifestyle with a lot of physical exercise is very important. In addition to the deficient oxygen transport caused by the anaemia, iron deficiency may also lead to disruption of cell division, myelination, cellular immune response and the oxidative metabolism.⁷ This may also become manifest in all kinds of symptoms. Iron deficiency may result in fatigue symptoms without anaemia being

involved, and patients with functional iron deficiency often suffer long periods of systemic inflammation.³

DIAGNOSIS AND TREATMENT OF IRON DEFICIENCY AND IRON DEFICIENCY ANAEMIA

Diagnosis of iron deficiency and iron deficiency anaemia Before bariatric surgery and for a long period thereafter, it is important to monitor the nutritional status of the patient. The possibility of iron deficiency is one thing to look out for during monitoring. The classic indicators of iron deficiency are serum ferritin ↓, serum iron ↓, TIBC ↑ (=total iron-binding capacity) or TSAT ↓ (transferrin saturation), and serum Hb ↓.¹³ The possibility of functional iron deficiency can best be detected by measuring the TSAT. After all, ferritin (stored iron) may be elevated if obesity or inflammation is involved, as a result of which relatively high iron levels can be interpreted wrongly.³ After bariatric surgery, the serum ferritin can in fact be an early indicator of disturbed iron absorption, as the iron stock is used up first before the TSAT decreases, after which the haemoglobin production decreases too.¹³

Treatment options for iron deficiency and iron deficiency anaemia

Iron deficiency can be treated with oral or parenteral iron supplements. The disadvantages of oral treatment are the disputed effectiveness, the long period before

effects are experienced³ and the poor therapy compliance, as well as gastrointestinal side effects (such as nausea and constipation).¹⁵ In addition, the release of iron from duodenal cells to the plasma is disturbed in patients who are severely overweight (see above). After malabsorptive interventions, the duodenal bypass reduces absorption of orally administered iron (see above). Oral iron supplements are therefore often ineffective for treating iron deficiency and iron deficiency anaemia after such bariatric interventions.^{3,9,14,16-18} A recent study showed that sufficient absorption of orally administered iron sulphate after RYGB surgery was observed in only one patient out of a group of 11.¹⁸ According to European guidelines, oral supplementation of micronutrients after bariatric surgery should only be used in a preventive regimen.¹⁹

Parenteral iron supplements are therefore recommended for correction of iron deficiency or iron deficiency anaemia after bariatric surgery.¹⁹ The disadvantages of intramuscular administration are the painful injection and skin discoloration.¹⁵ The most important advantage of intravenous iron is the rapid correction of iron deficiency and iron deficiency anaemia, and the fact that transport through the intestinal mucous membranes is avoided. The iron-polysaccharide complex is absorbed by the macrophages after parenteral administration.¹⁵ A relatively new intravenous iron preparation has been developed, because of the limitations associated with iron dextran and iron sucrose.²⁰ Ferric carboxymaltose (FCM) avoids dextran-inducing hypersensitivity reactions and overcomes

Table 2. Studies into the effects of intravenous iron (FCM; Ferinject) in iron deficiency (ID) and iron deficiency anaemia (IDA)

Study	ID and IDA associated with	Iron supplements	(Serum) parameters	Effectiveness of FCM	Incidence of side effects
Meta-analysis 14 studies ²²	Kidney diseases, IBD, post-partum, menorrhagia, heart failure	Intravenous FCM (n=2348) oral Fe (n=832) placebo (n=762) intravenous IS (n=384)	Hb, ferritin, TS	After 6-24 weeks: FCM versus oral Fe: % with normal Hb: 79 vs 62	SAEs same for FCM and oral Fe; constipation, diarrhoea, nausea and vomiting: more often with oral Fe
Randomised, open ²³	IBD	Intravenous FCM (n=240) intravenous IS (n=235)	Hb, ferritin, TS	FCM vs IS: % with Hb response ^{**} : 66 vs 54 (p=0.004)	FCM vs IS: 14 vs 11% Most frequent temporary AE (FCM): hyperferritinaemia, hyperphosphataemia
Randomised, double blind, placebo-controlled ²⁴	ID fatigue without anaemia	Intravenous FCM or placebo (n=290 premenopausal women)	Ferritin; TS, PFS score	FCM vs placebo: day 56 ↓ PFS score: 35% versus 19% (p<0.001) ferritin recovery: 99 vs 2%	Well tolerated

*11 randomised studies (including 3 double-blind placebo-controlled studies) and 3 cohort studies; **Hb increase ≥2g/dl (primary endpoint); FCM = ferric carboxymaltose; IBD = inflammatory bowel disease; IS = iron sucrose; PFS = Piper Fatigue Scale; (S)AEs = (serious) adverse events; TS = transferrin saturation.

the low-dosage limitations of iron sucrose. In contrast to the older preparations, FCM can be administered in one go (a maximum of 1000 mg iron) by rapid infusion and has a neutral pH and a physiological osmolarity. It is therefore a highly stable complex that does not release ionic iron under physiological conditions and does not provoke oxidative stress reactions. These characteristics mean that a test dose is not required beforehand and that FCM is relatively safe and offers convenience for patients.²¹

Numerous comparative clinical studies have now been performed for FCM, showing rapid correction of iron deficiency and a reduction of symptoms (*table 2*).

So far, there have been very few studies into the effect of intravenous supplements of iron after bariatric surgery. A retrospective analysis studied the effect of intravenous iron sucrose in 42 patients after bariatric surgery.¹⁴ These patients, who had been given oral iron supplements without success, responded successfully to intravenous iron supplements and their anaemia was alleviated. The frequency of intravenous iron supplements varied from once every four months to once every 11 months. In addition, various case reports have described how intravenous supplementation of iron in anaemic patients after bariatric surgery resulted in rapid and complete recovery of Hb values and iron parameters.³

Recommended iron supplementation in bariatric surgery

Over the last few years, iron supplements for bariatric patients have come to be seen as increasingly important. Any preoperative deficiency should be treated first, before surgery is performed. Iron levels should be checked regularly postoperatively. Because iron deficiency can develop years after bariatric surgery, lifelong checks are recommended.¹³

There are no specific guidelines in the Netherlands for treating iron deficiency and anaemia in bariatric patients. *Table 3* therefore contains an overview of recommendations for such treatment. It has been drawn up on the basis of the literature summary and the European guidelines on surgery for severe obesity.¹⁹ Iron supplements can be administered orally as a preventive policy. Usually, oral supplements are ineffective if the iron deficiency existed beforehand or is present after the bariatric surgery. Intravenous iron administration has a more rapid effect, causes fewer side effects and circumvents the now disrupted transport via the intestinal mucous membranes to the plasma. New intravenous iron preparations such as iron carboxymaltose are relatively safe, easy to use (one short infusion per treatment) and therefore cost-effective.

Table 3. Recommendations for iron supplementation for bariatric interventions based on international guidelines^{3,19} and a Dutch study⁵

	Blood values	Prevention and treatment of ID
Pre-operative	Iron, ferritin, TSAT, vitamin B ₁₂ , folate	Preventively: oral iron supplements, at least 65 mg/day (men) or 100 mg/day (women) When iron deficiency is present: intravenous iron infusion for rapid correction of the iron status
Post-operative	During checks*: iron, ferritin, TSAT, vitamin B ₁₂ , folate If necessary: calcium, vitamin D, copper, selenium and protein In the event of symptoms: also Hb, MCV *Regular checks: e.g. every 3 months during 1st year; every 6 months 2nd year and every year thereafter	Preventively: after surgery start oral iron supplements: at least 65 mg/day (men) or 100 mg/day (women), plus vitamin C If ID or IDA develops, despite oral iron supplements: intravenous iron supplements using short, high-dose infusion, e.g. single FCM dose of max. 1000 mg iron within 15 min
ID = iron deficiency; IDA iron deficiency anaemia; MCV= mean corpuscular volume; TSAT= transferrin saturation.		

CONCLUSION

Morbid obesity often leads to functional iron deficiency developing because increased cytokine production disturbs the transport from the intestinal mucous membranes to the plasma. In addition, bypassing the proximal part of the small intestine in malabsorptive bariatric interventions prevents iron absorption in that part of the small intestine. This explains why oral iron supplements are often ineffective for correcting iron deficiency and iron deficiency anaemia both before and after bariatric surgery. Intravenous iron administration has a more rapid effect, causes fewer side effects and circumvents the transportation from the intestinal mucous membranes to the plasma.

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