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ORIGINAL CONTRIBUTIONS

Iron Deficiency After Roux-en-Y Gastric Bypass: Insufficient Iron Absorption from Oral Iron Supplements

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Abstract
Background Roux-en-Y gastric bypass (RYGB) may reduce the absorption of iron, but the extent to which this absorption is impeded is largely unknown. First, we determined the prevalence of iron deficiency following RYGB and explored the risk factors for its development. Second, we examined to what extent oral iron supplements are absorbed after RYGB.
Methods Monocentric retrospective study in 164 patients (123 females, 41 males; mean age 43 years) who underwent RYGB between January 2006 and November 2010 was done. Pre- and postoperative data on gender, age, BMI, serum levels of iron, ferritin, hemoglobin, vitamin B_{12}, 25-hydroxy vitamin D, and use of proton pump inhibitors and H_2 antagonists were collected. Generalized linear mixed models were used for the analysis of the data. In 23 patients who developed iron deficiency after surgery, an oral challenge test with 100 mg $FeSO_4 \cdot 7H_2O$ was performed.
Results Following RYGB, 52 (42.3 %) female patients and 9 male (22.0 %) patients developed iron deficiency (serum ferritin concentration ≤20 μg/L). The prevalence of iron deficiency was significantly higher in females than males (p=0.0170). Young age (p=0.0120), poor preoperative iron status (p=0.0004), vitamin B_{12} deficiency (p=0.0009), and increasing time after surgery (p<0.0001) were also associated with iron deficiency. In the oral iron challenge test, only one patient out of 23 showed sufficient iron absorption.
Conclusions Iron deficiency is extremely frequent after RYGB and is linked with different risk factors. Iron supplementation seems essential, but the effect of oral tablets may be limited as absorption of oral iron supplements is insufficient post-RYGB.

Keywords Bariatric surgery · Iron deficiency · Oral iron supplements · Iron absorption

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Introduction

Over the last decades, there has been an increase in the prevalence of obesity, which is now considered a global epidemic [1]. As a consequence, the number of Roux-en-Y gastric bypasses (RYGB) performed has also surged, as it is currently the only intervention in combination with lifestyle modifications which achieves major and sustainable weight reduction [2]. However, RYGB may be associated with nutritional deficiencies [3]. Deficiencies in iron, vitamin B_{12}, folic acid, vitamin D, and calcium are the most common manifestations of nutritional problems post-RYGB, some of which can result in severe complications such as anemia [4–6]. Iron deficiency has been reported in 20 to 49 % of patients following RYGB [7, 8]. This deficiency can be explained by three factors: (1) diminished gastric acid secretion, which is necessary for the absorption of iron; (2) reduced intestinal absorption surface, particularly the

excision of the duodenum, the main absorption site of iron; and (3) low tolerance to red meat, a major source of iron [3, 9–11].

Therefore, patients after RYGB are routinely recommended to take prophylactic oral iron supplements [12]. Unfortunately, even upon correct administration of iron tablets, oral replacement therapy (usually with up to 300 mg of elemental iron per day in three or four iron tablets [13]) often fails to correct the deficiency in a large proportion of patients.

The objectives of the current study were twofold: (1) to determine the prevalence of iron deficiency post-RYGB and explore potential risk factors by evaluating the association between ferritin status and gender, BMI, age, time since surgery, medication use, and other vitamin deficiencies and (2) to assess absorption of iron after a standardized oral challenge test in iron-deficient patients after surgery.

Methods

Retrospective Analysis of Patient Records

The first part of the study (performed in March 2011) consisted of a retrospective analysis of records of patients who had undergone a RYGB between January 2006 and November 2010 in the University Hospitals Leuven, Belgium. In all patients, a laparoscopic gastric bypass with an alimentary limb of 120 cm and a small gastric pouch was performed.

For each patient, data were collected from the preoperative consultation and, dependent on the time of the surgery, from the consultations at 6, 12, 24, 36, 48, and 60 months postoperative, if available. There were no limits regarding gender or age. Patients who had undergone a previous bariatric surgery were excluded from the study.

The following parameters were included into the analysis: gender, age, BMI, serum levels of iron, ferritin, hemoglobin, vitamin B_{12}, and 25-hydroxy vitamin D. Furthermore, we included the use of proton pump inhibitors, H_2 antagonists, or antacids.

If the ferritin level at some point during follow-up (ranging between 6 and 60 months) was ≤20 μg/L, the patient was considered to suffer from iron deficiency. Anemia was defined as hemoglobin ≤12 g/dL in women and ≤14 g/dL in men, and vitamin B_{12} deficiency was defined as serum concentration of vitamin B_{12}≤180 ng/mL.

The study was approved by the Medical Ethics Committee of the University Hospitals Leuven.

Oral Challenge Test

Twenty-three patients from the retrospective study who had developed iron deficiency (ferritin level <20 μg/L) after RYGB, received an oral challenge test with 100 mg $FeSO_4 \cdot 7H_2O$ [14]. These oral iron absorption tests were conducted as a standard procedure in clinical practice before initiating intravenous iron. The patients did not use iron supplements and did not receive a transfusion of red blood cells during the 3 weeks preceding the oral challenge test. One week before the test, the use of proton pump inhibitors, H_2 antagonist, antacids, and vitamin supplements was discontinued.

Patients remained fasted during the entire test. In the fasted state (t=0), a blood sample was collected to determine serum iron, ferritin, transferrin, and transferrin saturation. Subsequently, a capsule containing 100 mg $FeSO_4 \cdot 7H_2O$ was administered with a glass of water. After the ingestion of iron, blood samples were taken at t=1, 2, and 3 h. The estimation of the extent of the intestinal absorption of iron was determined as the difference between the highest serum iron concentration obtained 1, 2, or 3 h following the ingestion of iron, and the serum iron concentration at t=0. An increase of 80 μg/dL was considered to be representative for sufficient iron absorption [14].

Statistical Analysis

Variables are summarized by means and standard deviations (SD). The data contain longitudinal measurements on the patients with assessments made at preoperative consultation and at 6, 12, 24, 36, 48, and 60 months postoperative. Nevertheless, not for all patients data are available at all time points due to missing information in files, missed consultations, or closing of data collection. Summary statistics are based on available data and restricted to records with available ferritin measurement. Generalized linear mixed models were used for the analysis of the data, with iron deficiency as binary response variable, and a random intercept accounting for correlation between repeated measurements coming from the same patient. Inference is likelihood-based and valid if drop-out is missing at random, in the sense that missingness may depend on previous outcomes or covariates but no further on unobserved outcomes [15]. Covariate effects are presented as odds ratios (OR) and their 95 % confidence intervals (CI). Effects were considered to be statistically significant when p<0.05. The analyses were performed using the NLMIXED procedure in SAS, version 9.2 of the SAS System for Windows.

Results

Prevalence of Iron Deficiency Post-RYGB and Predictive Parameters

Data from 164 patients were collected: 123 females (75.0 %) and 41 males (25.0 %), mean age of 43 years (SD 10 years), and mean BMI of 41.8 kg/m^2 (SD 4.9 kg/m^2). An overview of the clinical measurements at the different moments is shown in Table 1.

After surgery, 61 patients (37.2 %) developed iron deficiency at some point during follow-up after surgery (follow-up

Table 1 Summary statistics, shown as mean (standard deviation)

	Before surgery (n=130)	6 months after RYGB (n=107)	1 year after RYGB (n=90)	2 years after RYGB (n=55)	3 years after RYGB (n=44)	4 years after RYGB (n=27)	5 years after RYGB (n=19)
Gender	99♀, 31 ♂	86♀, 21 ♂	67♀, 23♂	39♀, 16♂	33♀, 11♂	18♀, 9♂	15♀, 4 ♂
Age (years)	43.1 (12.0)	42.2 (11.4)	42.1 (12.0)	44.3 (12.0)	42.4 (12.8)	43.6 (13.6)	41.2 (11.7)
Ferritin (μg/L)	101.7 (115.7)	81.3 (78.9)	76.9 (84.0)	66.3 (70.8)	35.6 (54.1)	56.2 (83.9)	38.4 (46.5)
Hemoglobin (g/dL)	14.0 (1.5)	13.4 (1.8)	13.3 (1.3)	13.3 (1.5)	13.5 (1.5)	13.5 (1.0)	13.5 (1.3)
Weight (kg)	117.6 (17.0)	86.5 (12.5)	80.2 (14.5)	84.8 (18.6)	90.2 (16.0)	98.7 (5.5)	75.4 (5.2)
BMI (kg/m^2)	42.0 (4.9)	30.9 (3.7)	28.6 (4.1)	29.5 (5.2)	31.6 (4.6)	36.5 (1.9)	26.7 (1.8)
Vitamin B_{12} (ng/mL)	301.0 (199.5)	270.9 (189.3)	264.5 (148.0)	266.8 (166.4)	317.2 (268.4)	261.5 (146.0)	361.4 (287.5)
Vitamin D (μg/L)	11.2 (13.3)	21.0 (13.0)	20.2 (12.9)	17.8 (11.1)	19.7 (11.4)	21.4 (13.9)	22.3 (17.5)

duration varying between 6 months and 5 years): 52 (42.3 %) female patients and 9 male (22.0 %) patients. The probability for males to develop iron deficiency post-RYGB was significantly lower compared to females [OR=0.18 (95 % CI 0.04–0.73); p=0.017]. Low iron status resulted in anemia in 15 out of 52 women (29 %) and 5 out of 23 men (22 %) post-RYGB.

This study also shows that the younger the patient, the higher is the probability for suffering from iron deficiency after RYGB [OR per year increase in age=0.94 (95 % CI 0.90–0.99); p=0.012]; this effect was the same in both sexes. Furthermore, patients with an existing iron deficiency before surgery had a much higher probability to suffer from iron deficiency postoperative compared to patients without a baseline iron deficiency [OR=19.49 (95 % CI 3.96–95.99); p=0.0004]. The prevalence of iron deficiency was also higher when patients had a vitamin B_{12} deficiency [OR=3.78 (95 % CI 1.74–8.21); p=0.0009], both the moments before and after RYGB.

The risk of developing iron deficiency post-RYGB increased over time [OR=1.06 (95 % CI 1.03–1.08) for 1 month increase; p<0.0001]; this trend was the same in both sexes. The prevalence of iron deficiency was considerably increased from 24 months after surgery onwards. Figure 1 shows the predicted probability of ferritin deficiency by time after the surgery.

There was no evidence for a relationship between the probability of developing iron deficiency and the amount of weight loss [OR=0.98 (95 % CI 0.96–1.01); p=0.13] or vitamin D deficiency [OR=0.60 (95 % CI 0.20–1.80); p=0.36]. When the group of patients who did take proton pump inhibitors or H_2 antagonists was compared with a group of patients who did not take any of this medication, no difference was found in developing iron deficiency [OR=2.27 (95 % CI 0.19–27.52); p=0.52]. An overview of the different associations is shown in Table 2.

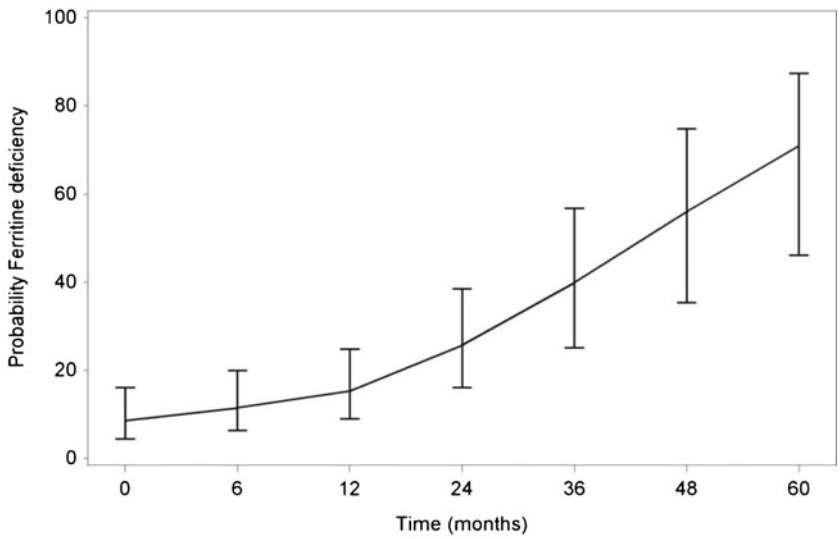

Fig. 1 Predicted probability of ferritin deficiency over time (with indication of 95 % confidence interval)

Table 2 Association between the development of iron deficiency and other parameters

Parameters	OR	95 % Confidence interval	*p* value
Gender: male versus female	0.18	0.04–0.73	0.0017
Age: 1 year increase	0.94	0.90–0.99	0.012
Baseline ferritin deficiency	19.49	3.96–95.99	0.0004
Vitamin B_{12} deficiency	3.78	1.74–8.21	0.0009
Time after surgery: increase by month	1.06	1.03–1.08	<0.0001
Weight loss	0.98	0.96–1.01	0.1271
Vitamin D deficiency	0.60	0.20–1.80	0.3620
Consumption of antacids: presence versus absence	2.27	0.19–27.52	0.5179

Oral Challenge Test

An oral iron challenge test has been performed in 23 patients (1 men and 22 women) suffering from iron deficiency post-RYGB (mean age 44 years, SD 11 years) with a mean ferritin of 7.7 μg/L. As shown in Fig. 2, there was only one patient who showed sufficient iron absorption (change in serum iron concentration >80 μg/dL). In four patients, the difference in serum iron concentration before and after the administration of the oral iron supplement was even lower than 20 μg/dL.

Discussion

Development of Iron Deficiency and Predisposing Factors

Thirty-seven percent of patients developed iron deficiency at some point after RYGB. Female gender, young age, poor preoperative iron status, vitamin B_{12} deficiency, and time after surgery were risk factors for the development of iron deficiency after RYGB. In our study, iron deficiency was more prevalent in women than in men which might be explained by menstrual loss in premenopausal women. Menstruation is often impaired in obese women prior to surgery, but usually resumes after RYGB contributing to iron loss and anemia [13, 16].

In line with the results of previous studies, we showed that iron deficiency is not only more prevalent in younger patients before bariatric surgery, but that young age also predisposes to iron deficiency after RYGB [17].

Another interesting finding is that preoperative poor iron status predisposes to iron deficiency after RYGB. This result clearly illustrates the need for an appropriate nutritional evaluation and screening of iron deficiency before RYGB. Consequently, patients should already be treated for iron deficiency before surgery to reduce the probability for developing postoperative iron deficiency and its possible complications [4, 18]. We also found that patients with vitamin B_{12} deficiency were also more likely to have iron deficiency. The link between iron and vitamin B_{12} deficiency can be explained by the reduced secretion of gastric acid and the decreased consumption of meat. Previous work of Avinoah et al. indicates that decreased meat consumption is probably the major factor that contributes to the development of iron and vitamin B_{12} deficiency after RYGB [11].

As shown, the risk of developing iron deficiency increases over time: 2 years post-RYGB, there were significantly more patients with iron deficiency compared to baseline. This is not surprising, as after RYGB, body iron stores gradually decrease [6, 18]. As a matter of fact, iron deficiency and subsequent anemia may develop years after the surgery. For that reason, patients require a lifelong follow-up of hematological and iron parameters, especially menstruating women, pregnant women, and adolescents, even after initial repletion of iron [16, 19–22].

We found no correlation between developing iron deficiency and the amount of weight loss, which is in line with a study of

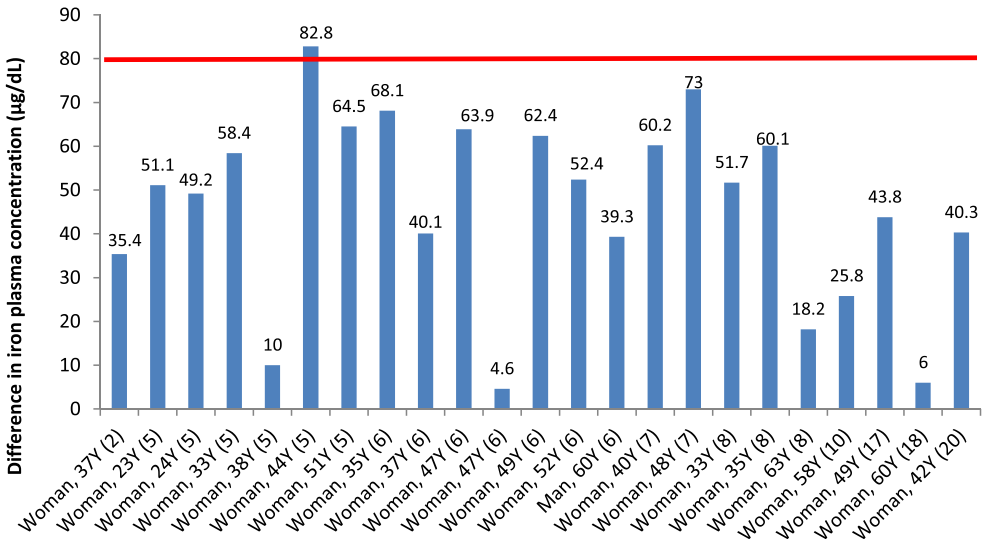

Fig. 2 The estimation of the extent of the intestinal iron absorption (expressed as the difference between the highest serum iron concentration after the administration of 100 mg $FeSO_4 \cdot 7H_2O$ and the serum concentration at $t=0$) for the 23 individuals who received the oral challenge test (including age (years) and serum ferritin levels (microgram per liter) (*between parentheses*))

Avinoah et al. [11]. Furthermore, there was no correlation between developing iron deficiency and vitamin D deficiency or with the use of proton pump inhibitors, H_2 antagonists, or antacids. Theoretically, these drugs may increase the risk of developing iron deficiency, as they reduce the acid secretion in the stomach and subsequent iron absorption [4]. A possible explanation for this lack of effect is that after RYGB the stomach is much smaller, which is associated with a reduced acid secretion. Therefore, these drugs may have less impact on acid secretion and iron absorption in patients after RYGB than in patients with a normal size of stomach, but this requires further investigation.

Unfortunately, we have no information on the use of vitamin supplements by the patients studied. This type of information is difficult to collect and can only be done in a prospective trial. Moreover, even when vitamins have been prescribed, compliance is very low.

Absorption of Oral Iron Supplements

In the oral challenge test, only one patient had an increase in plasma iron concentrations of more than 80 μg/dL after the administration of 100 mg iron sulfate. This means that in almost all patients who developed severe iron deficiency post-RYGB, the absorption of oral iron supplements is impaired. Previous studies have also shown that the absorption capacity for iron is reduced after RYGB and that oral iron supplements are often inadequate to correct iron deficiency [19–22]. However, to our knowledge, this is the first report of oral iron absorption tests in patients with severe iron deficiency after RYGB, demonstrating that the development of iron deficiency post-RYGB is largely due to an insufficient absorption of iron. Therefore we support the advice from other papers to switch oral iron supplements to parenteral iron therapy with iron dextran, ferric gluconate, or ferric sucrose if oral treatment is ineffective to correct iron deficiency [19, 21]. We do not know whether the absorption of oral iron supplements is also impaired in patients who do not develop iron deficiency after RYGB. Furthermore, a comparison of absorption of iron before and after surgery is not possible with these data, as the oral iron absorption tests have only been performed in patients after RYGB. So, further research on the absorption of oral iron is needed in order to determine whether it is effective to treat iron deficiencies post-RYGB initially with oral supplements or whether it is more useful for these patients to be directly treated with an intravenous formulation of iron to correct iron deficiency.

Conclusions

Iron deficiency is a frequent complication after RYGB, necessitating a good follow-up of these patients. Female gender, young age, preoperative poor iron status, vitamin B_{12} deficiency, and the time post-RYGB are predisposing factors for the development of iron deficiency. Iron supplementation seems essential in this population, but the effect of oral tablets may be limited as absorption of oral iron supplements is insufficient post-RYGB.

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Conflict of Interest The authors declare no conflict of interest.

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