Heme- and nonheme-iron absorption and iron status 12 mo after sleeve gastrectomy and Roux-en-Y gastric bypass in morbidly obese women[1–3]

Manuel Ruz, Fernando Carrasco, Pamela Rojas, Juana Codoceo, Jorge Inostroza, Karen Basfi-fer, Alejandra Valencia, Attila Csendes, Karin Papapietro, Fernando Pizarro, Manuel Olivares, Jamie L Westcott, K Michael Hambidge, and Nancy F Krebs

ABSTRACT

Background: The effect of bariatric surgery on iron absorption is only partially known.

Objective: The objective was to study the effects of sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGBP) on heme- and nonheme-iron absorption and iron status.

Design: Fifty-eight menstruating women were enrolled in this prospective study [mean ($\pm$SD) age: 35.9 $\pm$ 9.1 y; weight: 101.7 $\pm$ 13.5 kg; BMI (in kg/m^2): 39.9 $\pm$ 4.4]. Anthropometric, body-composition, dietary, and hematologic indexes and heme- and nonheme-iron absorption—using a standardized meal containing 3 mg Fe—were determined before and 12 mo after surgery. Forty-three subjects completed the 12-mo follow-up. Iron supplements were strictly controlled.

Results: Heme-iron absorption was 23.9% before and 6.2% 12 mo after surgery ($P < 0.0001$). Nonheme-iron absorption decreased from 11.1% to 4.7% ($P < 0.0001$). No differences were observed by type of surgery. Iron intakes from all sources of supplements were 27.9 $\pm$ 6.2 mg/d in the SG group and 63.2 $\pm$ 21.1 mg/d in the RYGBP group ($P < 0.001$). Serum ferritin and total-body iron decreased more after RYGBP than after SG.

Conclusions: Iron (heme and nonheme) absorption is markedly reduced after SG and RYGBP. The magnitude of the decrease in heme-iron absorption is greater than that of nonheme iron. The amounts suggested as iron supplements may need to be increased to effectively prevent iron-status impairment. This trial was registered at controlled-trials.com as ISRCTN31937503. *Am J Clin Nutr* 2012;96:810–7.

INTRODUCTION

Bariatric surgery has been shown to effectively treat sustained weight loss and to improve medical conditions in morbidly obese patients. This procedure includes many alternatives, such as adjustable gastric banding, sleeve gastrectomy (SG)[4], and Roux-en-Y gastric bypass (RYGBP) (1–5). Both SG and RYGBP have been shown to have highly satisfactory results; therefore, they are among the most common types of bariatric surgery currently performed (5). Iron deficiency and iron deficiency anemia are commonly reported after RYGBP and, although at a lesser extent, after SG (6, 7). Prophylactic iron supplements are routinely prescribed after these types of surgery, although there is no agreement on the amount and form of iron that could efficiently prevent the development of iron deficiency. In 2009 we presented

evidence on the effect of RYGBP on nonheme-iron absorption capacity, which indicated that iron absorption from a standard iron dose decreased at about one-third of the value observed before surgery (8). There are still some unanswered questions in this regard, such as the effects of type of surgery and whether such effects are distinct on the type of dietary iron (heme and nonheme).

The objective of this study was to examine the effects of SG and RYGBP on heme- and nonheme-iron absorption and iron status. We hypothesized that, in comparison with presurgical evaluations, iron absorption would be more affected after 12 mo of RYGBP than after SG. A secondary hypothesis was that, regardless of type of surgery, heme-iron absorption would decrease more than that of nonheme iron after surgery.

SUBJECTS AND METHODS

Subjects

Fifty-eight menstruating women were enrolled in this prospective study [mean ($\pm$SD) age: 35.9 $\pm$ 9.1 y; height, 1.59 $\pm$ 0.06 m; weight, 101.7 $\pm$ 13.5 kg; BMI (in kg/m^2), 39.9 $\pm$ 4.4]. The recruitment of patients began in March 2008 and lasted until December 2010. Sample size was calculated to detect a difference of 1.25 SD in iron absorption between the 2 groups. A flow

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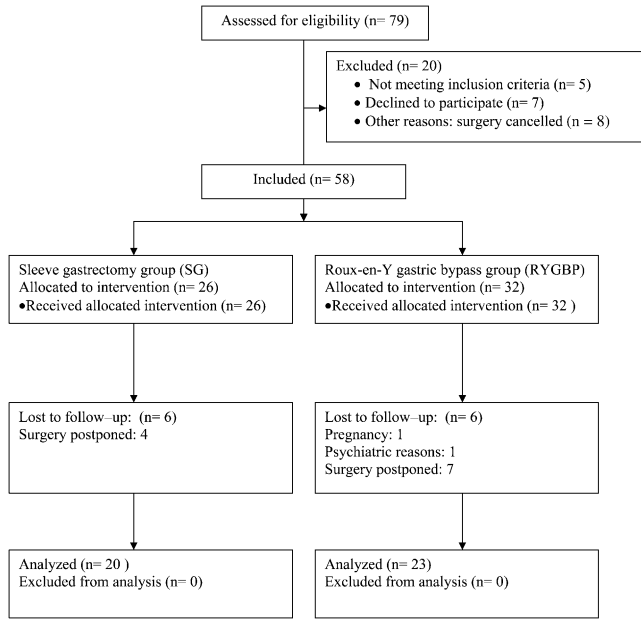
FIGURE 1. Flow diagram of volunteer recruitment and progress throughout the study.

diagram of volunteer recruitment and progress throughout the study is shown in **Figure 1**. The subjects were evaluated before and 6 and 12 mo after SG or RYGBP. Inclusion criteria considered women with a BMI $\geq$40 or a BMI $\geq$30 with comorbidities and who had decided to undergo RYGBP or SG at the Department of Surgery of the University Clinical Hospital. Forty-three subjects completed the 12-mo follow-up. Main initial anthropometric and hematologic characteristics of the individuals who abandoned the study were not significantly different from those who remained (data not shown).

All patients who accepted enrollment into the study signed an authorized informed consent form. The study was approved by the Ethics Committee for Human Investigation of the Faculty of Medicine of the University of Chile.

Experimental design

All patients followed the routine standard clinical procedures after surgery as defined by the Department of Surgery of the University of Chile Clinical Hospital that have been described elsewhere (8). During the first month, they were fed a liquid diet (500 mL/d) consisting of chicken breast, egg white, spinach, carrots, and potatoes that provided 800 kcal, 60 g protein, and 3.9 mg Fe among other nutrients. Patients who underwent SG received 1 tablet/d of a mineral-vitamin supplement (Centrum; Wyeth Laboratories) and a specially designed capsule containing additional iron (22 mg), zinc (8.5 mg), and copper (1.1 mg). Thus, the total iron supply was 36 mg/d, which represents $\sim$2 times the Recommended Dietary Allowance according to the reference values of the Institute of Medicine (9). Patients who underwent RYGBP received 1 tablet/d of a mineral-vitamin supplement (Maltofer vit; Andromaco Laboratories), which provides 60 mg elemental Fe, or the equivalent of 3 times the Recommended Dietary Allowance (9). In addition, patients from both groups received 1 tablet/d of a calcium supplement (Elcal D-PLUS; Andromaco Laboratories). The detailed composition of supple-

TABLE 1
Daily supply of selected micronutrients provided to obese women after SG and RYGBP[1]

	SG[2]	RYGBP[3]
Calcium (mg)	662	750
Magnesium (mg)	100	30
Zinc (mg)	15	25
Iron (mg)	36	60
Copper (μg)	1800	3000
Selenium (μg)	25	—
Manganese (mg)	2.5	5
Iodine (μg)	150	200
Chromium (μg)	25	50
Molybdenum (μg)	25	50
β-Carotene (mg)	600	—
Vitamin C (mg)	60	100
Vitamin E (mg)	15	30
Folic acid (μg)	200	1000
Thiamine (mg)	1.4	3
Riboflavin (mg)	1.6	3
Vitamin B-6 (mg)	2	10
Vitamin B-12 (μg)	1	10
Niacin (mg)	18	30
Biotin (μg)	150	100
Pantothenic acid (mg)	6	7
Vitamin A (μg)	600	1200
Vitamin D (IU)	600	800

[1] RYGBP, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

[2] The SG group received 1 tablet/d of Centrum (Wyeth Laboratories), 1 tablet/d of Elcal D-PLUS (Andromaco Laboratories), and a specially designed capsule containing additional iron (22 mg), zinc (8.5 mg), and copper (1.1 mg).

[3] The RYGBP group received 1 tablet/d of Maltofer vit and 1 tablet/d of Elcal D-PLUS (both from Andromaco Laboratories).

ments used in each group is presented in **Table 1**. At the medical evaluation carried out during the first week after surgery, 1 unit of vitamin/mo (TOL12; Saval Laboratories SA) was prescribed to all patients to be administered intramuscularly during the first 3 mo. This preparation contained 200 mg thiamine chlorhydrate, 100 mg pyridoxine chlorhydrate, and 10 mg hydroxycobalamin. One month after surgery, a solid diet divided in 5 or 6 meals was also prescribed. It provided $\sim$1000 kcal and 60 g protein. At the third month, the medical evaluation included hematologic tests. If the subjects had anemia or the risk of this condition, iron supplements were prescribed to be used during distinct periods of treatment. These procedures were repeated at 6 and 12 mo.

A careful record of the amount of iron contained in the supplements was kept throughout the study. This was carried out by a monthly record of pills provided by study protocol and by a count of those remaining in the container. Also, a periodic evaluation to determine any indication of iron supplements recorded in the medical record was made. If this situation occurred, the subject was contacted by telephone to determine the extent to which the indicated supplement had effectively been consumed.

Surgical procedures

Sleeve gastrectomy

This procedure involves removing 80% of the stomach. Gastric tubulization is performed starting 3–4 cm from the pylorus by

dividing the gastric corpus straight to the His angle applying two 4.8-mm nonopen cartridges and three to four 3.8-mm cartridges with an endoGIA stapler (Covidien), leaving a small gastric tubular pouch with a capacity of 80 to 100 mL (10).

RYGBP

If the patient had abnormalities on preoperative endoscopy or a family history of gastric cancer in a first-degree relative, a resectional gastric bypass was performed (11). It consisted of a 95% distal gastrectomy and resection of the distal stomach, which left a gastric pouch of 15 to 20 mL. An end-to-side gastrojejunostomy was performed with a circular stapler (N° 25). The length of the Roux-en-Y loop was 125–150 cm, according to the current practice of clinical centers in Chile, expressed in the 2005 panel of experts' consensus (12). The remaining patients underwent a similar procedure but with no resection of the distal excluded stomach (13).

Determinations

A series of anthropometric, dietary, and hematologic evaluations were conducted in all patients before the surgical procedure and 6 and 12 mo after SG or RYGBP. Body composition and heme-iron and nonheme-iron-absorption tests were carried out before and 12 mo after surgery.

Anthropometric and body-composition evaluations

Weight (kg) was measured to the nearest 0.1 kg on a digital scale (Seca; Vogel & Halke GMBH & Co), and height (m) was measured to the nearest 0.1 cm with a scale-mounted stadiometer according to standardized procedures (14). BMI (in kg/m^2) was calculated, and body fat mass and fat-free mass were measured by dual-energy X-ray absorptiometry with a Lunar DPX-L densitometer.

Dietary evaluation

During each evaluation period, the patients were interviewed by a dietitian, and a 3-d record that corresponded to 2 weekdays and 1 weekend day was completed. The data registered were analyzed by using the software Food Processor II (ESHA Research) to calculate energy and nutrient intakes. A database that contained locally generated nutrient composition data and information from the literature was used (15).

Iron-absorption tests

A pregnancy test was carried out before iron-isotope administration. On day 1 of the study, the subjects were fed 100 g of the standard liquid diet used during the first month after surgery, which was labeled with 37 kBq ^{59}Fe as ferric chloride and 111 kBq ^{55}Fe as heme iron. Labeled heme iron was obtained from concentrated erythrocytes from a calf according to a method described elsewhere (16). The iron content was adjusted to provide ∼3 mg Fe. On day 14, a fasting blood sample was obtained to assess iron-status indexes as indicated below and to measure circulating iron radioactivity with a liquid scintillation counter (Beckman LS-5000 TD; Beckman Instruments) according to the double-isotope method of Eakins and Brown (17). The percentage of iron absorbed was calculated on the basis of blood volume, which was estimated by using the Tulane tables (18) and assuming incorporation of 80% of the radioactive iron into red blood cells (19). Because blood volume in obese subjects is low in relation to actual body weight, we estimated blood volume according to a method previously proposed by us (8).

Hematologic evaluation

Hemoglobin and mean cell volume (MCV) were assessed by using a Coulter counter (CELL-DYN 1700; Abbott Diagnostics). Serum iron, total-iron-binding capacity, and transferrin saturation (TS) were determined by the method of Fischer and Price (20). Zinc protoporphyrin (ZPP) was measured by using a ZP Hematofluorometer (model 206D; AVIV Biomedical Inc). Soluble transferrin receptor (sTfR) was measured by using a commercial kit (ELISA; Ramco Laboratories Inc). Serum ferritin (SF) was assessed by using the method of the International Anemia Consultative Group (21). As a measure of subclinical inflammation, high-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetry (Quimica Clinica Aplicada). All women with hemoglobin concentrations <12 g/dL were classified as having anemia. Women with normal hemoglobin concentrations but with ≥2 abnormal biochemical measurements of iron status (MCV <80 fL or ZPP >70 μg/dL red blood cells or TS <15% or sTfR >8.3 mg/L or SF <12 μg/L) were classified as having iron deficiency. Those who had anemia plus ≥2 abnormal biochemical measurements of iron status were classified as having iron deficiency anemia.

Compliance

A new container with a known number of vitamin and mineral pills was provided to the women by a member of the research team at the beginning of every month throughout the study. At the time of distribution, the number of remaining pills from the previous month was counted. Compliance was assessed by comparing the total pills provided and those consumed during any given period.

Statistical analyses

Two-factor repeated-measures ANOVA with treatment group as a between-subjects factor and time as a within-subjects factor was used. When appropriate, the nonparametric Wilcoxon's signed-rank test was applied (22). Statistical analyses were performed by using SPSS 10.0 statistical software (SPSS Inc). Because SF, sTfR, hs-CRP, and iron-absorption data have skewed distributions, the values were converted to logarithms before any statistical analyses were performed. The results were then retransformed into antilogarithms to recover the original units and are expressed as geometric means + 1 SEM range.

RESULTS

Supplement compliance was 86.3 ± 8.4% (median: 86.1%) for the entire 12-mo period of the study. No differences were observed between groups. The main anthropometric data and dietary information for selected nutrients are shown in **Table 2**. Both heme and nonheme iron intakes decreased significantly during the study in both groups. Before surgery, heme iron intakes represented 10.8% and 12.6% of total dietary iron in the SG and RYGBP groups, respectively. The corresponding values after surgery were, on average, 12.9% and 13.6% in the SG and RYGBP groups, respectively. Iron intake from all sources of supplements during the 12-mo period were 27.9 ± 6.2 mg/d (range:

TABLE 2
Anthropometric characteristics and dietary intakes of obese women before and after SG and RYGBP[1]

| | Month 0 | | Month 6 | | Month 12 | | P[2] | |
	SG (n = 26)	RYGBP (n = 32)	SG (n = 20)	RYGBP (n = 25)	SG (n = 20)	RYGBP (n = 23)	Time effect	Time × group effect
Weight (kg)	96.4 ± 12.0	105.9 ± 13.3	70.9 ± 11.7	75.3 ± 8.6	67.0 ± 13.1	70.6 ± 9.9	<0.001	0.024
BMI (kg/m²)	37.3 ± 3.2	42.0 ± 4.2	27.5 ± 3.3	30.1 ± 3.5	26.0 ± 3.9	28.2 ± 4.0	<0.001	0.006
Fat mass (%)	44.3 ± 5.0	44.8 ± 3.4	—	—	29.8 ± 7.0	28.3 ± 6.9	≤0.001	0.271
Fat mass (kg)	43.0 ± 8.8	47.5 ± 8.0	—	—	20.6 ± 8.5	20.7 ± 7.2	<0.001	0.033
Energy intake (kcal/d)	2016 ± 656	1699 ± 506	899 ± 208	923 ± 183	1147 ± 301	1164 ± 382	<0.001	0.34
Protein intake (g/d)	78.1 ± 21.2	81.2 ± 31.1	52.4 ± 15.8	56.7 ± 13.1	59.0 ± 9.7	62.3 ± 16.8	<0.001	0.95
Vitamin C intake (mg/d)	68.4 ± 41.5	82.5 ± 83.8	59.2 ± 26.2	55.2 ± 21.4	73.4 ± 45.7	80.7 ± 56.3	0.054	0.55
Total iron intake (mg/d)[3]	13.9 ± 4.3	13.5 ± 4.4	6.8 ± 2.3	7.3 ± 2.4	8.8 ± 2.2	10.7 ± 5.8	<0.001	0.069
Heme iron intake (mg/d)	1.5 ± 0.7	1.7 ± 1.1	0.9 ± 0.6	1.1 ± 0.6	1.1 ± 0.5	1.3 ± 0.8	0.002	0.96
Nonheme iron intake (mg/d)	12.4 ± 3.9	11.8 ± 3.7	5.9 ± 2.0	6.2 ± 2.2	7.7 ± 2.0	9.4 ± 0.6	<0.001	0.69

[1] All values are means ± SDs. RYGBP, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.
[2] Repeated-measures ANOVA.
[3] Iron intake was exclusively from the diet.

14.7–37.2 mg/d) in the SG group and 63.2 ± 21.1 mg/d (range: 45.8–136.9 mg/d) in the RYGBP group ($P < 0.001$).

Before and 6 and 12 mo after surgery, a series of iron status–related indexes were determined, such as hemoglobin, MCV, ZPP, TS, sTfR, and SF. No differences in these variables were observed between groups before surgery ($P > 0.05$). A 2-factor repeated-measures ANOVA was conducted to test the effects of time and the interaction of time × group (SG compared with RYGBP) on these variables (**Table 3**). hs-CRP, an indicator of inflammation, was not associated with presurgery SF ($P = 0.29$). ZPP was increased during the experimental period, and, although a trend to a difference between groups was noted, it was not statistically significant. SF was lower 12 mo after surgery, and the change was greater in the RYGBP group ($P = 0.002$). hs-CRP was lower in both groups 6 and 12 mo after surgery ($P < 0.001$).

The number and percentage of subjects with abnormal iron-status indexes during the experimental period are shown in **Table 4**. A slight impairment of iron status was shown in the SG group. In contrast, a significant impairment of iron status was noted in the RYGBP group.

Another way to analyze changes in iron status is to calculate total-body iron, as suggested by Cook et al (23). Total-body iron decreased by 0.67 ± 3.9 and 2.56 ± 4.0 mg/kg 12 mo after surgery in the SG and RYGBP groups, respectively ($P = 0.10$). Nevertheless, when total-body iron was calculated on an absolute basis (body iron in mg/kg × body weight), it was shown that iron mass had decreased in both groups 12 mo after surgery and also that the decrease was more pronounced in the RYGBP group (−387.3 ± 269.7 mg) than in the SG group (−174.5 ± 285.0 mg) ($P = 0.017$).

The absorption of both types of iron diminished after surgery, although no differences were observed by group (**Figure 2**). Thus, consideration of both groups combined showed that heme-iron absorption before surgery was 23.9% (1 SEM range: 22.2–25.8%) and 12 mo after surgery was 6.2% (1 SEM range: 5.3–7.1%) ($P < 0.0001$). Nonheme-iron absorption before surgery was 11.1% (1 SEM range: 9.8–12.5%) and after surgery was 4.7% (1 SEM range: 3.1–5.5%) ($P < 0.0001$). Heme-iron absorption was significantly greater than nonheme-iron absorption before surgery ($P < 0.001$) but not after surgery ($P = 0.08$).

Correlation analyses between iron-absorption and iron-status indexes showed that heme-iron absorption was associated with SF only before surgery, ($r = -0.52$, $P < 0.001$), whereas non-heme-iron absorption was associated with SF ($r = -0.57$, $P < 0.001$) and with MCV ($r = -0.27$, $P = 0.045$), ZPP ($r = 0.31$, $P = 0.02$), and TS ($r = -0.28$, $P = 0.04$). After surgery, the association between heme-iron absorption and SF disappeared. Heme-iron absorption was associated with MCV ($r = -0.46$, $P = 0.002$), and nonheme-iron absorption was associated with hemoglobin ($r = -0.33$, $P = 0.034$), MCV ($r = -0.60$, $P < 0.001$), ZPP ($r = 0.46$, $P = 0.002$), TS ($r = -0.64$, $P < 0.001$), sTfR ($r = 0.40$, $P < 0.001$), and SF ($r = -0.70$, $P < 0.001$).

DISCUSSION

Since earlier reports (24) and up to recent years (25, 26), iron deficiency has been a common feature of bariatric surgery, especially after restrictive-malabsorptive procedures such as RYGBP and biliopancreatic diversion. Prophylactic iron is routinely recommended. The American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery (AACE/TOS/ASMBS) suggest the use of 45 to 60 mg/d. They point out, however, that in some cases this may not be enough and may lead to the administration of intravenous forms of iron (27, 28). SG was initially introduced as a first-step procedure to minimize the surgical risk of patients with a BMI >55, followed by RYGBP (29). Nevertheless, this procedure has been increasingly used on its own in patients with a BMI <50, because of its satisfactory results at ameliorating comorbidities (5, 30). Furthermore, SG is now commonly used in patients with less severe forms of obesity, leaving procedures such as RYGBP for those with greater BMI. This procedure is not exempt of complications, such as micronutrient deficiencies (31), although the magnitude is less than that observed in RYGBP (7, 32). In purely restrictive procedures, such as SG, the AACE/TOS/ASMBS states that there is less need for nutritional supplementation.

In our study, the amounts of supplementary iron were well in agreement with those suggested by the AACE/TOS/ASMBS (27.9 mg/d in the SG group and 63.2 mg/d in the RYGBP group

TABLE 3
Iron-status indexes and high-sensitivity C-reactive protein in obese women before and after SG and RYGBP[1]

| | Month 0 | | Month 6 | | Month 12 | | P[2] | |
	SG (n = 26)	RYGBP (n = 31)	SG (n = 20)	RYGBP (n = 24)	SG (n = 19)	RYGBP (n = 23)	Time effect	Time × group effect
Hemoglobin (g/dL)	13.4 ± 1.2[3]	13.2 ± 1.1	13.6 ± 0.8	12.9 ± 1.3	13.5 ± 1.1	12.5 ± 1.8	0.22	0.44
Mean cell volume (fL)	85.3 ± 4.6	85.4 ± 4.8	86.0 ± 4.3	86.0 ± 7.3	86.3 ± 4.9	83.8 ± 7.4	0.19	0.25
Zinc protoporphyrin (μg/dL RBCs)	71.4 ± 11.7	71.9 ± 19.9	75.7 ± 16.9	90.5 ± 42.2	72.2 ± 15.4	93.4 ± 45.2	0.023	0.064
Transferrin saturation (%)	22.0 ± 9.7	25.3 ± 10.9	25.4 ± 7.7	21.9 ± 9.8	30.7 ± 12.4	23.6 ± 16.9	0.12	0.19
Soluble transferrin receptor (mg/L)	4.7 (4.3–5.1)[4]	5.2 (4.8–5.6)	4.7 (4.3–5.2)	4.3 (3.9–4.7)	4.7 (4.2–5.3)	3.8 (3.4–4.3)	0.27	0.31
Serum ferritin (μg/L)	23.7 (20.4–27.6)	33.7 (30.8–36.9)	22.2 (18.7–26.4)	17.2 (13.8–21.4)	20.4 (16.5–25.1)	12.5 (9.7–16.1)	<0.001	0.016
High-sensitivity C-reactive protein (mg/L)	5.9 (5.1–7.0)	4.4 (3.5–5.4)	1.4 (0.9–2.0)	0.3 (0.2–0.5)	0.8 (0.6–1.2)	0.2 (0.1–0.3)	<0.001	0.139

[1] RBCs, red blood cells; RYGBP, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.
[2] Repeated-measures ANOVA.
[3] Mean ± SD (all such values).
[4] Geometric mean; + 1 SEM range in parentheses (all such values).

on average). Despite this, the iron indexes and the amount of total-body iron showed a mild (SG group) and moderate to severe (RYGBP group) impairment of iron status, which suggests that such amounts were not enough to prevent iron deficiency. In terms of the interpretation of changes in iron-status indexes during the experimental period, 2 limitations in our study design must be pointed out: *1*) the presence of subclinical inflammation, as indicated by an hs-CRP concentration >5 mg/L, in about half of the subjects before surgery, which may have resulted in an underestimate of abnormal baseline ferritin values (33), and *2*) the use of the Cook algorithm to calculate total-body iron (23), because such a method was developed in a nonobese population. However, we concluded that these limitations did not invalidate the major trends and conclusions involving the iron-status indicators.

Iron homeostasis is largely dependent on iron absorption (34, 35). Baseline heme- and nonheme-iron absorption were within the range reported in other studies (16, 36). Iron absorption takes place at its greatest extent in the duodenum and initial portions of the jejunum. Incorporation of heme and nonheme iron into the enterocyte occurs through distinct mechanisms. Heme iron is released from hemoglobin and myoglobin by proteolytic enzymes in the stomach and small intestine, and a specific transporter (heme carrier protein 1) in the apical surface of the enterocyte takes up the heme molecule, which is later degraded by heme oxygenase-1–releasing iron to the soluble iron pool (37, 38). Nonheme iron must be in the ferrous form to be taken up by the divalent metal transporter 1, also known as divalent cation transporter 1 (39). Therefore, the activity of reducing agents such as ascorbic acid and the brush border membrane cytochrome duodenal cytochrome b reductase are crucial (37). Recent evidence by Theil et al (40), who studied the absorption of ferritin, indicates the presence of a second nonheme iron uptake process—endocytosis. Regardless the mechanism of incorporation into the enterocyte, iron in the soluble cytoplasm follows a common pathway, it is either stored or transported to the serosal side for its release mediated by ferroportin and oxidation by hefestin for further transport by plasma transferrin (37). Thus, iron absorption is affected by the type of iron, dietary factors that may enhance or inhibit iron uptake, enterocyte function, and systemic factors such as hypoxia, erythropoiesis, and mainly the size of iron stores (37, 41). A peptide (hepcidin) secreted by hepatocytes in amounts proportional to body iron stores regulates iron absorption by interacting with the iron efflux transporter ferroportin in enterocytes (37, 41).

Alterations of the digestive tube anatomy have profound effects on iron-absorption capacity, as shown by a previous study from our group in which we documented that iron absorption after RYGBP was ~30% of the value observed before surgery (8).

Two relevant issues need to be addressed to complement and expand knowledge on this subject. One is the potential effect of a purely restrictive procedure (SG) compared with a restrictive-malabsorptive procedure (RYGBP) on iron absorption and iron status, and the other is whether the effect of these types of surgery affect heme- and nonheme-iron absorption differently. In relation to the latter, we had postulated that the absorption of heme iron would be more affected than that of nonheme iron, which was corroborated by the experimental data. A major feature of both SG and RYGBP is the dramatic reduction in stomach size;

TABLE 4
Subjects with abnormal iron-status indexes before and after SG and RYGBP[1]

	Month 0		Month 6		Month 12	
	SG	RYGBP	SG	RYGBP	SG	RYGBP
Hemoglobin <12 g/dL [n/N (%)]	5/26 (19.2)	3/31 (9.7)	0/20 (0.0)	3/24 (12.5)	3/20 (15.0)	9/23 (39.1)[2,3]
Mean cell volume <80 fL [n/N (%)]	1/26 (3.8)	3/31 (9.7)	1/20 (5.0)	1/24 (4.2)	1/20 (5.0)	6/23 (26.1)[3]
Zinc protoporphyrin >70 μg/dL RBCs [n/N (%)]	11/26 (42.3)	15/31 (48.4)	13/20 (65.0)	17/24 (70.8)	13/20 (65.0)	16/23 (69.6)
Transferrin saturation <15% [n/N (%)]	4/25 (16.0)	2/31 (6.5)	1/20 (5.0)	5/24 (20.8)[2]	2/20 (10.0)	8/23 (34.8)[2,3]
Soluble transferrin receptor >8.3 mg/L [n/N (%)]	2/25 (8.0)	3/31 (9.7)	3/20 (15.0)	2/24 (8.3)	3/19 (15.8)	3/23 (13.0)
Serum ferritin <12 μg/L [n/N (%)]	5/25 (19.2)	0/31 (0.0)[4]	3/20 (15.0)	9/24 (37.5)[2]	6/20 (30.0)	10/23 (43.5)[2]
IDA [n/N (%)][5]	2/25 (8.0)	2/31 (5.0)	0/20 (0.0)	3/24 (12.5)	2/19 (10.5)	7/23 (30.4)[2]

[1] IDA, iron deficiency anemia; RBCs, red blood cells; RYGBP, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.
[2] Percentage of abnormal values, within each group, are significantly greater than those at month 0, $P < 0.05$ (Wilcoxon's signed-rank test).
[3] Percentage of abnormal values at month 12 are significantly different between study groups, $P < 0.05$ (Mann-Whitney U test, 1-tailed).
[4] Percentage of abnormal values at month 0 are significantly different between study groups, $P < 0.05$ (Mann-Whitney U test, 2-tailed).
[5] Defined as hemoglobin <12 g/dL plus abnormal values for ≥2 indexes.

therefore, an immediate consequence is a reduction in food–gastric juice interaction. Gastric juice is crucial to the release of heme from dietary hemoglobin and myoglobin (35), and it has a role in the release of nonheme iron from its protein matrix and in the solubilization and ionization of dietary iron (42). Besides, intraluminal inhibiting and enhancing factors are more relevant to nonheme-iron absorption that to heme-iron absorption (34, 35). To the best of our knowledge, no previous studies have evaluated heme-iron absorption after bariatric surgery.

Because a major component of RYGBP, in addition to stomach reduction, is the exclusion of the duodenum and a portion of the jejunum, we expected that iron absorption after SG would be less affected than after RYGBP. The results, however, did not show differences in iron absorption between the groups. To explain this apparent paradoxic result, we must consider at least 2 elements: one related to the relative capacity of distinct segments of the intestine to absorb iron and their ability to adapt to increased iron-transfer demands and another related to the design of the absorption tests carried out in our study. In animal models, iron transfer in the duodenum is 3 times that in the jejunum and 6 times that in the ileum (43). These authors also studied adaptations after ileoje-junal transposition; they reported that transposed enterocytes took up some jejunal characteristics in terms of transferred iron, although jejunal values were not reached (44). McKie et al (45) studied the expression of genes involved in iron metabolism. They found a gradient of mucosal nonheme iron (duodenum > jejunum > ileum) and regional differences in ferritin and transferrin receptor mRNA abundance. Although quantitatively less than the duodenum, but not quite different from the jejunum and ileum, segments of the large intestine (cecum and proximal colon) are also able to absorb iron, according to the observations of Blachier et al (46) and Bouglé et al (47). Thus, after RYGBP, patients may have some degree of adaptation to the exclusion of duodenum and part of the jejunum, which may have been potentiated by an increased iron-absorption stimulus as a result of the greater reduction in iron stores than in those undergoing SG. On the other hand, absorption tests were carried out by using a 3-mg Fe dose in the test diet, which is widely used in iron-absorption studies that compare foods or iron sources (48). Because we did not observe differences in the magnitude of the decrease in iron absorption between the SG and RYGBP patients after 12 mo of surgery, although iron status was more affected in

the latter, we speculated that both groups were able to handle such an iron dose in a relatively similar way, but the maximal capacity of iron transfer may have been different. To test such a possibility, iron-absorption tests should be carried out by using
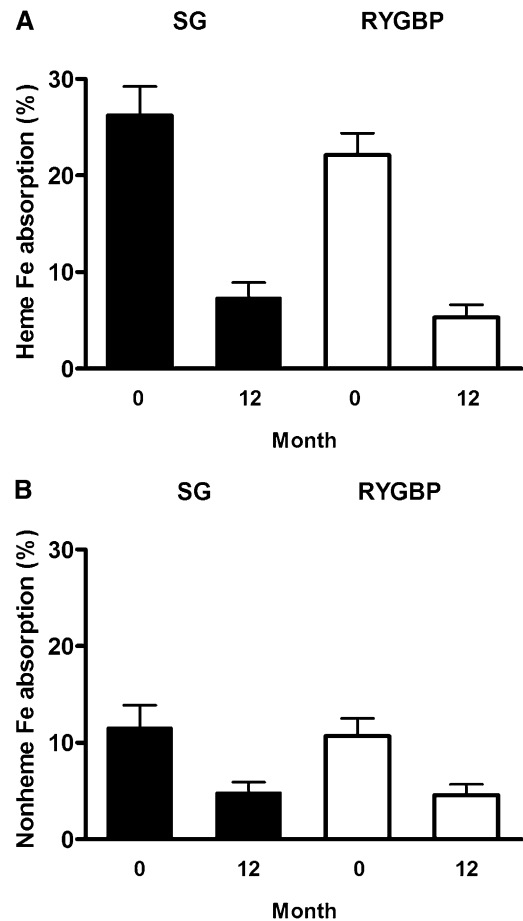

FIGURE 2. Geometric mean (±1 SEM) heme-iron (A) and nonheme-iron (B) absorption from a standard meal before and after 12 mo of SG (A and B: $n = 18$; dark bars) and RYGBP (A: $n = 23$; B: $n = 21$; open bars). The data were analyzed by repeated-measures ANOVA. Heme-iron absorption: time effect, $P < 0.0001$; time × group effect, $P = 0.275$. Nonheme-iron absorption: time effect, $P < 0.0001$; time × group effect, $P = 0.620$. RYGBP, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

much larger doses of iron. Unfortunately, this was not possible to implement in our subjects.

In conclusion, iron (heme and nonheme) absorption decreased markedly after SG and RYGBP. The magnitude of the decrease in heme-iron absorption was greater than that of nonheme iron. The amount of iron supplementation suggested may need to be increased to effectively prevent iron-status impairment.

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