Anemia after bariatric surgery cannot be explained by iron deficiency alone: results of a large cohort study

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Abstract

Background: We sought to identify the frequency and mechanisms of anemia after bariatric surgery in a bariatric surgery program at the Medical College of Wisconsin, Milwaukee, WI. Anemia after bariatric surgery has often been attributed to iron deficiency, although an inflammatory component might be present, making the anemia after surgery mechanistically complex.

Methods: The body mass index and hemoglobin (Hb), vitamin B12, folate, iron, and ferritin levels were extracted from the records of 1125 patients for 4 years after Roux-en-Y gastric bypass. Anemia was defined using the World Health Organization criteria.

Results: The mean body mass index, Hb, and ferritin decreased after surgery. The body mass index decreased from 50.1 kg/m² (95% confidence interval [CI] 49.6–50.6) at baseline to 33.0 kg/m² (95% CI 32.3–33.6) at 12 months and remained unchanged thereafter. The Hb level decreased from 13.4 g/dL (95% CI 13.3–13.5) to 12.8 (95% CI 12.6–13.1) and ferritin from 87.5 ng/mL (95% CI 75.2–99.7) to 55.4 (95% CI 42.9–68.0) at 24–48 months, and serum iron increased from 68.4 g/dL (95% CI 66.8–70.0) to 82.8 (95% CI 76.4–88.7); all P values were <.01. Anemia was present in 12% (95% CI 10–14%) of patients at baseline and had increased to 23% (95% CI 16–30%) at 24–48 months. The changes in ferritin, Hb, and the percentage of patients with anemia were most pronounced in premenopausal women. Vitamin B12 and folate levels were unaffected.

Conclusion: The baseline incidence of anemia was greater than expected and increased significantly after surgery. The percentage of those with anemia and low ferritin was most significant in premenopausal women; however, the overall iron bioavailability improved significantly with pronounced weight loss, suggesting a reduction in inflammation. These findings indicate that anemia after bariatric surgery cannot be explained on the basis of iron availability and suggest that other mechanisms, currently undefined, contribute to the development of anemia in these patients. (Surg Obes Relat Dis 2011;7:151–156.) © 2011 American Society for Metabolic and Bariatric Surgery. All rights reserved.

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In the present report, we have provided an analysis of 1125 morbidly obese patients who underwent Roux-en-Y gastric bypass performed at a single center and followed up for ≤4 years with an assessment of hemoglobin (Hb), serum iron, ferritin, vitamin B₁₂, and folate. The objective was to identify the incidence of anemia after bypass surgery in a vitamin-supplemented and tightly followed cohort, as recommended by the National Institutes of Health and the European task force guidelines [9,10]. We found that, compared with the National Health and Nutrition Examination Survey (NHANES) data [11], the percentage of anemia adjusted for age and gender at baseline was greater than expected. The percentage of anemia increased from 12% to 23% after 24–46 months and the ferritin and Hb levels decreased significantly. The changes were most pronounced in premenopausal women. Unexpectedly, the serum iron level increased in all patient groups, suggesting improved bioavailability with decreasing inflammation through weight loss. Although iron deficiency remains important, inflammation in the morbidly obese, combined with rapid weight loss, could affect the iron metabolism in a complex, yet poorly understood, fashion.

Methods

**Patient population**

The prospectively collected records of 1125 patients (126 men and 999 women) in the Bariatric Surgery Program at the Medical College of Wisconsin were evaluated for a maximum of 48 months (range 3–48) postoperatively. The body mass index (BMI) and Hb, vitamin B₁₂, folate, serum iron, and ferritin levels were determined at baseline and at 3, 6, 12, 18, 24, 36, and 48 months postoperatively. No patient was excluded from the analysis. Women aged <50 years were considered premenopausal, because the population and NHANES data have indicated that most of these women would still be menstruating [11,12]. The length of time after surgery at analysis and the loss to follow-up determined the availability of the values for analysis. The Medical College of Wisconsin’s institutional review board approved the data acquisition and patient confidentiality safeguards.

**Anemia definition**

Anemia was defined by the age- and gender-specific World Health Organization criteria (Hb <12 g/dL in women and <13 g/dL in men).

**Surgical procedure**

Retrocolic Roux-en-Y gastric bypass was performed using an open or a laparoscopic approach. To create the Roux limb, the ligament of Treitz was identified and the jejunum divided 20 cm distally. The distal jejunal limb was measured for a distance of 75–150 cm, at which point, the proximal jejunum was stapled, creating the jejunojejunostomy. The Roux limb was brought up to the stomach in a retrocolic fashion, a 10–15 cm³ gastric pouch was created, and a hand-sewn gastrojejunostomy was completed.

**Micronutrient supplementation**

All patients were supplemented orally with 1 daily multivitamin containing iron (18 mg), folic acid (400 μg), vitamin B₁₂ (1000 μg), and calcium citrate with vitamin D (1500 mg).

**Statistical analysis**

A comparative analysis was done for each variable at baseline and at different points postoperatively using the Student t test for the hypothesis that the mean difference compared with baseline would be significantly different from 0. For ferritin, the values before surgery and 3 months postoperatively were combined (no statistically significant differences present) and defined as the baseline because of the large number of patients without measurements before surgery. For the same reason, the values obtained at 24–48 months were combined. For the binary variables (the presence of anemia), McNemar’s test determined whether a significant difference was present between the proportion of anemic patients at baseline and each point thereafter. For all tests, 95% confidence intervals (CIs) were computed. A 5% false discovery rate was calculated according to the Benjamini-Hochberg procedure. Using this criterion, results with P <.0237 were considered significant.

**Results**

**Demographics**

A total of 1125 patients (mean age 42 years [95% CI 41.3–42.5] and mean BMI 50.1 kg/m² [95% CI 49.6–50.6]) underwent Roux-en-Y gastric bypass. Of the 1125 patients, 126 were men (mean age 44 years [95% CI 42.4–45.9] and mean BMI 53.8 kg/m² [95% CI 51.4–54.7]) and 999 were women. Of the 999 women, 758 were premenopausal (mean age 37 years [95% CI 36.6–37.7] and mean BMI 50.1 kg/m² [95% CI 49.4–50.7]) and 241 were postmenopausal (mean age 55 years [95% CI 54.8–55.9] and mean BMI 48.5 kg/m² [95% CI 47.5–49.5]).

**Changes in BMI and Hb**

The mean BMI of all patients decreased significantly from 50.1 kg/m² [95% CI 49.6–50.5] at baseline to 33.0 kg/m² (95% CI 32.3–33.6) at 12 months postoperatively (P <.01) without significant changes thereafter (Fig. 1A). Although the mean BMI differed significantly between patient groups at baseline and at various follow-up points (P <.01), the relative decrease in BMI compared with baseline was similar for all the groups. The mean Hb decreased significantly...
from 13.4 g/dL (95% CI 13.3–13.5) at baseline to 12.8 g/dL (95% CI 12.6–13.1) at 24–48 months ($P < .0001$). The base-line mean Hb level differed significantly among the groups. It was greatest in the men (14.7 g/dL), followed by the postmenopausal (13.4 g/dL) and premenopausal women (13.2 g/dL; $P < .01$; Fig. 1B). For each group, the mean Hb was significantly lower at 24–48 months than at baseline ($P < .0001$). The relative decrease in the mean Hb level was significantly more pronounced for premenopausal women than for postmenopausal women or men ($P < .01$).

**Frequency of anemia**

At baseline, 12% (95% CI 10–14%) of patients were anemic, with similar percentages of anemic patients in each group (9% of men and 12% of women in each group). The

![Fig. 1. Mean decreases in (A) BMI and (B) Hb at 24–48 months after Roux-en-Y gastric bypass were significant for all patient groups compared with baseline ($P < .0001$). Although no relative difference in weight loss was found among patient groups, the relative decrease in Hb in premenopausal women was significantly greater than in postmenopausal women or men ($P = .01$). Error bars represent standard error of mean.](image1)

![Fig. 2. Percentage of anemic patients before and after Roux-en-Y gastric bypass. (A) Percentage of anemia had increased significantly in all patients at 24–48 months compared with baseline ($P = .01$). (B) Percentage of anemic patients was greater in premenopausal women than in postmenopausal women; the difference was statistically significant at most follow-up points. Error bars represent standard error of mean.](image2)
percentage of anemia had increased to 21% (95% CI 16–27%) and 23% (95% CI 16–30%) at 18 and 24–48 months, respectively (all \( P < .01 \)). The increase in anemia remained significantly greater in premenopausal women than in postmenopausal women, and while a significant decrease in serum iron was only apparent at baseline and disappeared postoperatively, with overall increases in serum iron. Error bars represent standard error of the mean.

Change in serum ferritin and serum iron

As depicted in Fig. 3A,B, the mean ferritin level decreased continuously postoperatively and was significantly lower at 24–48 months (55.4 ng/mL, 95% CI 42.9–68.0) than at baseline (87.5 ng/mL, 95% CI 75.2–99.7; \( P < .01 \)). In contrast, the mean serum iron level had increased significantly (baseline 68.4 µg/dL, 95% CI 66.8–70.0) at 24–48 months postoperatively (82.8 µg/dL, 95% CI 76.4–88.7; \( P = .0003 \)). Before increasing, the serum iron level had decreased significantly to 61.0 µg/dL (95% CI 59.2–62.9; \( P < .0001 \)) at 3 months. The relative decreases in ferritin and increases in iron were similar for the pre- and postmenopausal women. However, although a significant difference in ferritin levels was always present between the 2 groups, the differences in serum iron were only present at baseline (Fig. 3C,D).

The men had significantly greater mean ferritin levels (155.3 ng/mL, 95% CI 111.9–198.8, \( n = 33 \)) at baseline than the women (69.3 ng/mL, 95% CI 60.1–79.8; \( P < .0001 \)). Unlike the decreases in the women (Fig. 3C), the decrease in ferritin for the men was not significant at 24–48 months (102.3 ng/mL, 95% CI 50.8–153.7, \( n = 16 \)), possibly because of the small patient numbers. Similar results were found for the mean serum iron levels, which were significantly greater in the men (76.7 µg/mL, 95% CI 71.9–81.5, \( n = 109 \)) than in the women (67.4 µg/mL, 95% CI 65.6–69.0; \( P < .0003 \)) at baseline. However, unlike for the women (Fig. 3D), the increase was not statistically significant (82.2 µg/mL, 95% CI 71.4–99.6, \( n = 18 \)).

Changes in serum folate and vitamin B12

Postoperatively, the mean folate and vitamin B12 levels had increased significantly from 15.7 ng/mL (95% CI 15.3–16.1; \( n = 792 \)) and 427 pg/mL (95% CI 416–438; \( n = 964 \)) at baseline to 17.5 ng/mL (95% CI 16.7–18.4; \( n = 147 \)) and 626 pg/mL (95% CI 572–680; \( n = 148 \)) at 24–48 months \( (P < .01) \), respectively. No age- or gender-related differences were found.

Discussion

We assessed 1125 patients before and after Roux-en-Y gastric bypass for the prevalence of anemia and the depletion of body iron stores, folate and vitamin B12 levels. A pronounced weight loss from a mean BMI of 50.1 to 33.0

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Fig. 3. Changes in mean serum ferritin and iron after Roux-en-Y gastric bypass. For ferritin, baseline corresponds to data collected ≤3 months postoperatively. (A) Mean ferritin levels had decreased significantly at 24–48 months postoperatively \( (P < .01) \) compared with baseline. (B) Mean serum iron levels had increased significantly after initial postoperative rapid decrease \( (P < .0001) \). (C) Mean ferritin levels remained significantly greater in premenopausal women than in postmenopausal women, while a significant decrease in serum iron was only apparent at baseline and disappeared postoperatively, with overall increases in serum iron. Error bars represent standard error of the mean.
kg/m² within 12 months postoperatively ($P < .01$) was accompanied by significant decreases in Hb and ferritin and significant increases in serum iron after an initial decrease at 3 months. We also observed significant increases in folate and vitamin B₁₂. As previously suggested [13], deficiencies of those vitamins can, therefore, be excluded as important reasons for anemia after bypass surgery.

The decreasing ferritin and increasing serum iron levels were surprising because the iron levels will be low in patients with iron-deficiency anemia. In the absence of inflammation, ferritin is a direct measure of the body iron stores and, if low in conjunction with low serum iron levels, indicates iron deficiency. However, ferritin is also an acute phase reactant, and the quantitation of iron stores become unreliable in the presence of inflammation [14].

Inflammation has been increasingly recognized as a pathophysiologic hallmark of obesity [15]. Weight loss after bariatric surgery has yielded a significant decrease in inflammatory markers such as C-reactive protein, haptoglobin, and white blood cell count in association with increasing transferrin saturation [16–18]. Therefore, lower ferritin levels after bariatric surgery might be related to reduced inflammation, in addition to the depletion of iron stores. The improvement in serum iron seen in our study might indicate improved iron bioavailability through decreased inflammation. The significant decrease in the serum iron level at 3 months could be ascribed to the increased inflammation relatively soon after surgery. Decreased iron absorption shortly after gastric bypass was recently reported [8], with a trend toward improvement thereafter and stable normal transferrin saturation levels throughout.

Inflammation upregulates hepcidin, a peptide that decreases iron absorption and releases iron from stores [19]. Hepcidin is upregulated in adipose tissue [20]. Serum hepcidin is elevated in obese women compared with matched nonobese controls [21]. Most recently, a significant decrease in hepcidin and inflammatory markers (interleukin-6, C-reactive protein) after gastric banding was reported in conjunction with improved “functional iron profiles” [22].

In premenopausal women, however, iron depletion remains an important problem. Overall the percentage of anemia increased significantly from 12% at baseline to 23% at 24–48 months. The increase in anemia was particularly marked in the premenopausal women, with the percentage of anemia remaining stable in the men and improving significantly during the first 12 months in the postmenopausal women before returning toward baseline. Ferritin decreased significantly and at the same rate in both groups of women. However, premenopausal women had the lowest baseline values which reached ferritin levels compatible with iron deficiency in the presence of inflammation (<50 ng/mL) [23] early at 6–12 months postoperatively. The initial significant improvement in the percentage of those with anemia for postmenopausal women might be a function of improved iron bioavailability and iron store depletion thereafter.

Inflammation could also explain the greater-than-predicted anemia in our patients before surgery. The NHANES studies [11] have demonstrated that women in their childbearing years (aged 17–49 years) have a greater prevalence of anemia than men (12.2% versus 1.5%) and that, after 50 years of age, the differences between women and men disappear, with the percentage of anemia approaching approximately 5% for both populations. In our cohort, women aged <50 years (12% anemic) matched their respective NHANES group but men (9% anemic) and women aged ≥50 years (12% anemic) exceeded the expected ranges. At least 3 other studies found a high prevalence of anemia (≤22%) in morbidly obese patients before weight reduction surgery [7,24,25]. Two of these studies demonstrated an association between an elevated BMI with elevated ferritin levels [7,24].

Mild decreases in Hb (0.5–1 g/dL), such as were seen in our study, have been reported after bariatric surgery [8], even in the absence of iron deficiency [26,27] and remain currently unexplained.

To know the true incidence of iron deficiency or anemia of inflammation requires concurrent measurements of iron, the total iron-binding capacity, and ferritin at each observation point. The patient numbers with complete values at all follow-up points would have been too small for meaningful analyses, and we also might have positively selected for good compliance and health. The results from our study population cannot be extrapolated to all those with morbid obesity and are only representative of the subset that chose and was able to undergo surgical bypass surgery. The analysis of women aged <50 years versus ≥50 years was arbitrary. However, large population data have indicated a premenopausal status for the vast majority of women aged <50 years [11,12]. The menstrual history was not recorded, and the results could have been affected if a significant proportion of women considered premenstrual in our population had ceased menstruation prematurely.

We, and others [7,8], found that in the modern era of bypass surgery, approximately one quarter of patients will experience anemia, lower than the historical cohorts in the 1980–1990s, during which anemia was reported to be ≥50% [4,5]. Reinforcement of vitamin supplementation according to the National Institutes of Health and European task force guidelines [9,10] and close follow-up at bariatric centers might be instrumental. Routine iron supplementation was begun after surgery, with >80% compliance recorded in our population (data not shown). A combination of inflammation reduction and iron store depletion might be responsible for the decrease in ferritin. Increased iron bioavailability with decreasing ferritin levels could be explained by the decreasing inflammation and might compensate partially for the reduced absorptive capacity, especially in the men and older women in whom the balance was not.
challenged by the cyclical blood loss. However, normal serum iron levels with decreasing ferritin levels could still be a precursor to iron deficiency, and anemia and ferritin levels less than normal would clearly indicate iron deficiency [14]. In contrast to postmenopausal women or men, premenopausal women with increased iron demands seem to have the greatest propensity for early depletion of iron stores and anemia. Routine vitamin supplementation with low doses of iron in multivitamin formulations (usually <20 mg/pill) might not suffice for menstruating women. In general, the changes in iron metabolism and Hb in the obese and after bariatric surgery are complex and incompletely understood. Translational studies of iron metabolism, inflammation, and the role of adipose tissue are required to characterize “the anemia of obesity.” An improved understanding of the complex changes in iron metabolism after weight loss surgery that go beyond simple iron deficiency will be critical to further improve the outcomes in bariatric patients.

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Disclosures

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