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Annette von Drygalski and Deborah A. Andris
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Invited Review

Anemia After Bariatric Surgery: More Than Just Iron Deficiency

Annette von Drygalski, MD, PharmD1; and Deborah A. Andris, MSN, APNP2

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Bariatric surgery for morbid obesity is rapidly gaining popularity. Restrictive and/or malabsorptive surgical interventions result in dramatic weight loss with significantly decreased obesity-related morbidity and mortality. Anemia, which may affect as many as two-thirds of these patients, is of concern and generally thought to be caused by iron deficiency. Although iron deficiency in this population may be frequent given pouch hypoacidity, defunctionalized small bowel, and red meat intolerance, it may not account for all anemias seen. First, there is increasing evidence that obesity creates a state of chronic inflammation. Both iron deficiency anemia and anemia of chronic inflammation present with low serum iron levels. Most studies reporting anemia after bariatric surgery lack serum ferritin determinations so that the relative contribution of inflammation to anemia cannot be assessed. Second, a significant number of anemias after bariatric surgery remain unexplained and may be attributable to less frequently seen micronutrient deficiencies such as copper, fat-soluble vitamins A and E, or an imbalance in zinc intake. Third, although deficiencies of folate and vitamin B12 are infrequent, study observation periods may be too short to detect anemia attributable to vitamin B12 deficiency because vitamin B12 storage depletion takes many years. This review is intended to increase awareness of the mechanisms of anemia above and beyond iron deficiency in the bariatric patient and provide healthcare providers with tools for a more thoughtful approach to anemia in this patient population. (Nutr Clin Pract. 2009;24:217-226)

Keywords: bariatric surgery; anemia; anemia, iron deficiency; obesity; inflammation; micronutrients

Morbid obesity has become a serious health problem and is epidemic in the Western world. Obesity is determined by body mass index (BMI), which describes the body weight relative to height (kg/m²) and in adults correlates strongly with the total body fat content.1 A BMI of 30-34.9 is considered as class 1 obesity, 35-39.9 as class 2, and ≥40 as class 3. Morbid obesity is usually defined as a BMI ≥40, or a BMI ≥35 in combination with comorbidities, and is an indication for bariatric surgery.2 More than one-third of the U.S. population is obese and approximately 5% are morbidly obese.3 Obesity is associated with substantial morbidity and mortality; life expectancy can be decreased by up to 20 years in severe obesity.4,7

Diet and exercise are widely advocated but have been essentially ineffective in achieving meaningful weight loss in the morbidly obese population. Sustained excess body weight loss of no more than 10% has been reported with conventional weight loss programs but achieves only mild effects on obesity-related comorbidities.8-14 In contrast, a recent meta-analysis of 136 studies with 22,094 patients who had undergone bariatric surgery demonstrated that the mean percentage of excess weight loss was 61.2%. Restrictive procedures like gastric banding yielded lower mean excess body weight loss (47.5%) compared with combined restrictive and malabsorptive procedures like Roux-en-Y gastric bypass (68.2%). Thirty-day surgical mortality was low, ranging from 0.1% to 1.1% for the different procedures.15 There is convincing evidence that bariatric surgery not only results in dramatic improvement of medical conditions such as sleep apnea and other hypoventilation syndromes, type 2 diabetes mellitus, obesity-related cardiomyopathy, and hypertension, hyperlipidemia, asthma, pseudotumor cerebri, osteoarthritis, back pain, female urinary incontinence, and infertility16-27 but also substantially decreases obesity-related and overall mortality.28,29

Bariatric surgery is becoming increasingly popular as a powerful means for weight reduction and correction of obesity-related morbidity and mortality. From 1990 to 2000, the rate of bariatric surgery in the United States increased nearly 6-fold, from 2.4 to 14.1 per 100,000 adults (P = .001), and the number of bariatric surgeries has almost doubled over the past 3 years. Whereas approximately 100,000 procedures were performed in 2003, the estimated numbers for 2006 were 175,000-200,000.30-32
Micronutrient and vitamin deficiencies following bariatric surgery are of concern despite oral supplementation. Deficiencies can persist because of restricted intake, food intolerance, poor eating habits, and diminished absorptive capacity. Published incidences vary substantially but have been reported to be as high as 64% for vitamin B₁₂, 33% for folate, 51% for vitamin D, 34% for vitamin C, 11% for vitamin A, 18% for vitamin B₆, 14% for vitamin B₂, and 18% for vitamin B₆. Clinical manifestations include osteoporosis, neuropathy, xerophthalmia, nyctalopia, and Wernicke's encephalopathy; in addition, neural tube defects in offspring have been described in case reports and case series. These abnormal conditions seem disproportionately rare given the relatively high frequency of vitamin deficiencies. In contrast, the development of iron deficiency has been described as a major cause of anemia following bariatric surgery. In many instances, however, the study methodology is a retrospective analysis of case series and often devoid of complete evaluation of patients' iron status or of other possible causes of anemia. With this review, we hope to orient healthcare providers to the problem of anemia in bariatric patients, create an understanding regarding the rigors of healthcare providers to the problem of anemia in bariatric patients, and alter gastric emptying. Restrictive procedures carry the highest risk for nutrition deficiencies because they significantly alter digestion and malabsorption of protein, vitamins (both fat and water soluble), and minerals. There are usually 3 main components of these surgeries: a partial gastrectomy, the common or nutrient limb, and the biliopancreatic limb. The common limb is a 50- to 100-cm portion of distal small bowel where limited digestion and absorption occur, whereas the biliopancreatic limb is created from the remainder of the proximal small bowel and functions to divert digestive juices to the nutrient or common limb. The Roux-en-Y gastric bypass (RYGB), currently the preferred and most frequently performed procedure in the United States, results in both restriction and malabsorption. The stomach is separated with a stapler and a 15-mL pouch is created. The small intestine is divided, and the distal stomach, duodenum, and first part of the divided jejunum are bypassed. The distal end of the jejunum is anastamosed to the pouch (gastro-jejunostomy) to allow for emptying while the proximal end is connected side-to-side to the jejunum (jejuno-jejunostomy) creating a 75- to 150-cm Roux limb. For illustrations of surgical techniques, we refer the reader to a comprehensive review by Andris.

Mechanisms of Anemia

The incidence of anemia following bariatric surgery has been reported to be as high as 74% and has been mostly ascribed to iron deficiency. The development of iron deficiency anemia (IDA) following bariatric surgery has been attributed to a combination of several factors. First, the duodenum and proximal jejunum are the sites of physiological iron absorption and are effectively excluded from the digestive tract when surgical bypass techniques are used. However, increasing the length of defunctionalized jejunum from 75 cm to 150 cm by using RYGB bypass technique does not result in higher percentages of postsurgical IDA despite a significantly greater percentage of excess weight loss. Second, the gastric pouch is hypoacidic, decreasing the bioavailability of oral iron as well as the optimal function of iron transport molecules.
meat intolerance is encountered in >50% of bariatric patients even >4 years after surgery.44,49 Red meats are rich in iron and heme iron is easily absorbed, although its transport mechanisms are poorly understood. Fourth, when physiological iron demands exceed iron absorption, as in menstruating females, the continued depletion of body iron stores will result in IDA.

Two other micronutrients whose deficiency can cause anemia are vitamin B₁₂ and folate. Similar to iron, the bioavailability of vitamin B₁₂ is dependent on hydrochloric acid in the stomach. Hydrochloric acid facilitates cleavage of vitamin B₁₂ bound to food. Just as gastric acid–blocking agents have been shown to result in decreased serum vitamin B₁₂ levels,62 gastric acid production following bariatric surgery is low and protein-bound vitamin B₁₂ absorption will decrease.65,66 In addition to the mechanisms facilitated by hydrochloric acid, absorption of vitamin B₁₂ in the terminal ileum requires the presence of intrinsic factor produced by the parietal cells of the stomach. Lack of intrinsic factor causes pernicious anemia. However, despite suboptimal conditions for vitamin B₁₂ bioavailability in bariatric patients, vitamin B₁₂ deficiency following surgery has not been described as a major clinical problem. Two reasons might account for that. First, vitamin B₁₂ body stores are usually sufficient to prevent the onset of vitamin B₁₂ deficiency for many years, and mean study observation times following bariatric surgery usually only range between 2 and 4 years. Second, high-dose oral vitamin B₁₂ supplementation has been shown to be at least as effective as parenteral supplementation in pernicious anemia, in other vitamin B₁₂-deficiency states, and even after total gastrectomy. In one study, a dose of 2000 mcg of oral vitamin B₁₂ given daily was compared with 1000 mcg intramuscular vitamin B₁₂ on days 1, 3, 7, 10, 14, 21, 30, 60, and 90. After 120 days, patients who received oral therapy had significantly higher serum vitamin B₁₂ levels than patients who received parenteral therapy.65-68 The pathway that leads to vitamin B₁₂ absorption independent of intrinsic factor and intact terminal ileum is poorly understood. Up to 1% of large doses of oral vitamin B₁₂ can be absorbed by this unknown mechanism.65 Vitamin B₁₂ is contained in oral multivitamin supplements that are usually administered following bariatric surgery, and there is good evidence that bariatric patients respond well to vitamin B₁₂ supplementation.45

The primary reason for folate deficiency is decreased dietary intake of folate. Folate is predominantly absorbed in the upper third of the small intestine, but absorption can occur along the entire part of the small intestine when necessary, such as after surgical procedures.49 Although varying incidences of folate deficiency have been reported in the very early days following bariatric surgery (0%-38%),70-72 folate deficiency, like vitamin B₁₂ deficiency, has become rare in the modern era of vitamin supplementation and nutrition support. In fact, increased rather than decreased folate levels following bariatric surgery have been reported recently.45 Other than regular vitamin supplementation, the suggested mechanism for maintaining folate status under achlorhydric conditions is increased bacterial folate synthesis in the upper small bowel.73

Iron, folate, and vitamin B₁₂ are micronutrients whose deficiencies come to mind first as causes of anemia after bariatric surgery. The majority of cases of anemia are ascribed to iron deficiency; however, in many instances, the definition of IDA is not provided in published reports or is inaccurate. Frequently, the diagnosis is made solely on grounds of low serum iron levels, and information about serum ferritin levels is missing. Serum ferritin is an important parameter for the assessment of total body iron stores and is also necessary to distinguish IDA from anemia of chronic inflammation (ACI), which may play a role in obesity. Serum iron levels are low in both types of anemia and therefore are not distinctive. Whereas in IDA the depletion of body iron stores leads to low serum ferritin concentration (≤40 ng/mL), in ACI serum ferritin is often elevated (≥200 ng/mL). Serum ferritin levels between 40 and 200 ng/mL combined with low serum iron levels require clinical interpretation and suggest coexistence of IDA and ACI (Table 1).74 Serum ferritin is an acute phase reactant and marker of inflammation. As opposed to intracellular ferritin within the reticuloendothelial system or liver, where iron is stored to support red cell production, serum ferritin is free of iron. A low serum ferritin level reflects low body iron stores and is diagnostic for iron deficiency. In the presence of inflammation, serum ferritin is elevated as an acute phase reactant independent of iron trafficking. The recently discovered peptide hepcidin is responsible for blocking intestinal iron absorption as well as iron release from stores during inflammation.75 Hepcidin is up-regulated by interleukin-6, which together with other inflammatory cytokines and proteins like tumor necrosis factor-α, von Willebrand factor, C-reactive protein, and fibrinogen, is elevated in obese patients.76 The new concept of inflammation in obesity makes the distinction of IDA and ACI in bariatric patients important. Because only IDA can be corrected readily with iron supplementation, inflammation may explain to some extent the unresponsiveness to oral iron and the high percentage (10%-50%) of unexplained anemia seen in bariatric surgery patients in some reports.75,46,77,78

More than a decade ago, Brolin et al45,46 evaluated the "hematological parameters" folate, vitamin B₁₂, iron, total iron-binding capacity, and transferrin saturation in 2 cohorts with >400 adults followed up to 5 years after RYGB. The authors found that microcytosis, which in conjunction with hypochromia can be considered the morphological hallmark of IDA, was only present in about half of the patients with low serum iron and anemia. The authors concluded that this anemia could not be explained by iron
deficiency alone.45,46 In addition, only half of the patients who were self-reportedly compliant corrected their anemia with oral iron supplementation. In contrast, patients who developed vitamin B12 or folate deficiencies could easily be corrected with oral multivitamin supplementation. Eighty-one percent of the vitamin B12-deficient patients and almost all folate-deficient patients responded,46 indicating that the absorption of vitamin B12 and folate is much less affected than iron absorption. Because the oral bioavailability of vitamin B12, folate, and iron following bariatric surgery is restricted by some of the same conditions, such as hypochlorhydria and reduced intestinal surface, additional impairment of iron transport in the intestinal wall through inflammation is likely. Ferritin was not assessed in either study and might have provided important diagnostic information. Impairment of iron absorption suggestive of inflammation has also been demonstrated in 55 obese bariatric patients with a mean BMI of 30 kg/m² (±6 kg/m²). In this study, all patients had low serum ferritin levels (≤29 mcg/dL) consistent with some degree of iron deficiency. However, the patients with abnormal iron absorption tests (19/55) had significantly higher ferritin concentrations than those patients with normal iron absorption (12.2 vs 7.2 mcg/L; P = .001), suggesting underlying inflammation.79

Preoperative Anemia

Four recently published studies addressed various nutritional and clinical parameters prior to surgical bypass or banding in the morbidly obese (BMI ≥ 40 kg/m²). There was a very high proportion of people who were anemic according to World Health Organization criteria (up to 22%), even after exclusion of thalassemia as a cause of anemia in 1 Greek study.44,54,80 Three of the studies provide more detail and are discussed briefly here.

In the study by Ernst et al,81 a significant increase in the prevalence of anemia was observed with increasing BMI. Serum ferritin level (pmol/L) was generally high and averaged 132.5 ± 122.0, 171.1 ± 169.4, 200.5 ± 193.4, and 142.4 ± 143.1 at BMIs of 35-39, 40-44, 45-49, and ≥50, respectively.81 In the study by Skroubis et al,81 presurgical evaluation of another 243 obese patients who were to undergo either RYGB without BPD when their BMI was <50 kg/m² (morbidly obese; mean BMI 45.6 kg/m²) or with BPD if their BMI was ≥50 kg/m² (super obese; mean BMI 57.2 kg/m²) revealed that 18.1% of the morbidly obese and 16.8% of the super-obese patients were anemic. Both groups were well balanced in regard to the number of premenopausal females and males. Ferritin levels were significantly higher in the super-obese compared with levels in the morbidly obese (71.6 vs 41.4 ng/mL; P = .0004). The percentage of patients with serum ferritin levels <9 ng/mL was lower in the super-obese when compared with the morbidly obese (6.5% vs 16.4%), and this difference became statistically significant 2 years after surgery (15.2% vs 37.7%). Percentage weight loss within the 2 groups was identical (approximately 35%).84 In the study by Flanchbaum et al,80 presurgical evaluation of 379 consecutive patients undergoing RYGB (mean BMI 51.8 kg/m²) revealed that 22% of patients were anemic. Low serum iron concentration was detected in 44% of all patients without differences among females and males (42% vs 54.4%; P = .08). Low ferritin levels, which would indicate iron deficiency, were present in only 9.9% of females and were not present in males and, curiously, anemia was more prevalent in males than females (40.7% vs 19.1%; P < .005).80

Information about the prevalence of anemia associated with low or high serum ferritin concentration in association with low serum iron concentration was not provided in the preceding studies. However, serum ferritin levels generally seem to be high in obese people, and inflammation may be causative of anemia in a substantial number of patients. At least presurgically, iron deficiency seems to be a minor problem.

Other Micronutrient Deficiencies Causing Anemia

Similar to vitamin B12 deficiency, copper deficiency can cause hematological abnormalities with or without neurological complications such as ataxia, myelopathy, and neuropathy. Copper absorption is thought to take place in the upper GI tract, but precise location and mechanisms are incompletely understood.82 Prior to 1970, copper deficiency had been described anecdotally as a cause of anemia and neutropenia in malabsorption syndromes.83-88

### Table 1. Definition of Iron Deficiency Anemia (IDA) and Anemia of Chronic Inflammation (ACI)

<table>
<thead>
<tr>
<th></th>
<th>IDA</th>
<th>ACI</th>
<th>ACI+IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Low (≤40 mcg/dL)</td>
<td>Low (≤40 mcg/dL)</td>
<td>Low (≤40 mcg/dL)</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Low (≤20%)</td>
<td>Low (≤20%)</td>
<td>Low (≤20%)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Low (≤35 ng/mL)</td>
<td>High (≥200 ng/mL)</td>
<td>In between (36–199 ng/mL)</td>
</tr>
</tbody>
</table>

**Notes:**

As suggested by Weiss and Goodnough.74

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**Definition of Iron Deficiency Anemia (IDA) and Anemia of Chronic Inflammation (ACI)**

- **IDA**
  - Low serum iron concentration
  - Low transferrin saturation
  - Low ferritin level

- **ACI**
  - Low serum iron concentration
  - Low transferrin saturation
  - Low ferritin level

- **ACI+IDA**
  - Low serum iron concentration
  - Low transferrin saturation
  - High ferritin level

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*As suggested by Weiss and Goodnough.*74
the 1980s, it was recognized that some patients receiving long-term parenteral nutrition developed copper deficiency, and formulas were adjusted accordingly.\textsuperscript{89,90} More recently, several cases of copper deficiency resulting in anemia and/or neurological complications following bariatric surgery have been described.\textsuperscript{91-93} Beyond these case reports, 2 retrospective case series provide further insights. In the first study, 26 patients were evaluated for neurological deficits that arose after bariatric surgery. Copper levels were only available in 8 of the 26 patients, but, of those, 5 patients were found to be copper deficient with no other micronutrient deficiencies apparent. The most prominent presentation was posterolateral myelopathy. Hematological parameters were not assessed.\textsuperscript{94} In the second study, 40 patients with hematological abnormalities attributable to copper deficiency were reviewed. Sixty percent of patients had undergone bariatric surgery or other surgery involving the GI tract, most commonly gastric resection. Macrocystic anemia (median hemoglobin of 10.6, median mean corpuscular volume of 99.6) and neutropenia were the most frequent abnormalities with neurological manifestations (mostly myeloneuropathy) present in the majority of patients. Abnormalities observed on bone marrow examination included vacuoles in myeloid precursors, iron-containing plasma cells, a decrease in granulocyte precursors, and ring sideroblasts, mimicking myelodysplastic syndrome.\textsuperscript{95} In both studies, there was a wide variation in latency periods from surgery to diagnosis, reaching from weeks to several decades. Hematological and neurological manifestations seemed to appear simultaneously approximately 1-2 years prior to the final diagnosis. From the current literature, it is impossible to estimate the incidence of copper deficiency following bariatric surgery. Serum copper and ceruloplasmin levels as well as 24-hour urine copper excretion are not part of routine anemia evaluations. Signs and symptoms of overt copper deficiency, prompting more in-depth evaluation, occur many years after surgical intervention. Because bariatric surgery is a relatively young albeit rapidly growing field, more evidence may accumulate over the next few years.

Zinc can affect copper absorption and result in anemia when ingested in excess. Serum analysis in cases where zinc toxicity was suspected revealed increased zinc and decreased copper and ceruloplasmin levels. Patients’ bone marrow findings were reminiscent of copper deficiency.\textsuperscript{96} The interferences of zinc, copper, and iron are poorly understood. On a molecular level, several mechanisms may contribute. Zinc causes up-regulation of metallothionein in intestinal cells. Metallothionein can bind and trap copper, which may lead to depletion of copper stores through continuous sloughing of intestinal cells.\textsuperscript{97} Divalent ions including zinc, copper, and the ferrous form of iron are shuttled from the apical to the basolateral intestinal cell membrane by divalent metal transporter 1 (DMT1), which is most notably expressed on the luminal duodenal surface.\textsuperscript{98} Iron deficiency results in up-regulation of DMT1, and absence of DMT1 causes profound iron deficiency in animals, indicating that it is the major channel for absorption of elemental iron in the intestinal wall.\textsuperscript{99} Although copper, zinc, and iron seem to share the same transmembrane transport molecule, it remains unknown how their transport is orchestrated. Imbalance of dietary divalent ions may challenge such shared transport mechanisms and may lead to metabolic disturbances. Because copper is an integral part of the ferroxidases ceruloplasmin and haephestin, which convert ferrous (Fe2+) to ferric (Fe3+) iron during export at the basolateral membrane of intestinal cells and also during export from nonintestinal cells like macrophages, its deficiency may limit bioavailable iron for red cell production.\textsuperscript{60}

It is well known that deficiencies of vitamin B\textsubscript{12} and folate (which are both water soluble) can lead to anemia, but the association of anemia with other vitamin deficiencies is less clear. In the Western world, where access to fruit, vegetables, and animal products is less problematic, severe deficiencies of vitamins A and E (which may play some role in the development of anemia) are rarely encountered. However, in the developing world, where the prevalence of anemia can reach 50% in certain areas,\textsuperscript{100} vitamin A deficiency in malnourished individuals has been linked to anemia independent of other factors such as human immunodeficiency virus (HIV) infection, iron deficiency, malaria, sickle cell disease, and bacterial infections.\textsuperscript{101,102} The role of vitamin E deficiency in anemia is also not well defined, but such a deficiency was suggested to contribute to anemia in a small group of patients with malabsorption caused by cystic fibrosis.\textsuperscript{103} The mechanisms by which vitamin A and E deficiencies might cause anemia are poorly understood. Whereas vitamin A may affect erythropoiesis by stimulation of erythropoietin production,\textsuperscript{104} the antioxidant properties of vitamin E have been implicated in red cell survival.\textsuperscript{105,106} Although several studies suggest improvement of anemia with vitamin supplementation,\textsuperscript{107-109} data are conflicting.\textsuperscript{110} Because vitamin A has been shown to improve nonheme iron absorption and iron availability from stores,\textsuperscript{107,111} it is plausible that vitamin A deficiency could exacerbate the development of anemia in bariatric patients where iron intake and metabolism are altered.

**Practice of Vitamin and Mineral Supplementation**

Practice patterns of vitamin and mineral supplementation following bariatric surgery vary widely. A recent survey sent to 236 surgeons (of which 109 returned the completed questionnaire) demonstrated that most surgeons
administer multivitamins, but additional supplementation with oral iron and vitamin B₁₂ was only prescribed by 63% and 49% of surgeons who answered to the questionnaire, respectively. Although most surgeons routinely obtained complete blood counts postoperatively, serum iron, folate, and vitamin B₁₂ levels were only assessed by 56%, 58%, and 66% of surgeons, respectively. The surgeons’ estimates as to the frequencies of vitamin deficiencies encountered in their patient populations were low compared with the published prevalences.¹¹²

No standardized nutrition guidelines are available for use in bariatric surgery. The most recently developed interdisciplinary European guidelines on surgery for severe obesity recommend follow-up every 3 months after the operation in the first postoperative year, every 6 months in the second year, and annually thereafter. Minimal laboratory evaluations include serum liver function tests, a complete blood cell count, serum levels of vitamin B₁₂, vitamin D, parathyroid hormone, bone alkaline phosphatase, ferritin, calcium, albumin, transferrin, creatinine, prothrombin time, and urine analysis. Lifelong daily vitamin and micronutrient supplementation, including vitamins A, D, E, and K as well as calcium, is recommended. Additional supplementation should be adjusted according to the patient’s laboratory test results. Specific instructions for iron supplementation are not provided.¹¹³ Comparable recommendations for North America, although less detailed, can be derived from the Bariatric Research Consortium at the National Institutes of Health at http://www.niddk.nih.gov/fund/crfo/may2002-council/rfac502_1.htm.

Multivitamin supplementation may be the standard of care in institutions researching micronutrient deficiencies following bariatric surgery. Many published studies explicitly mention vitamin and micronutrient supplementation as part of their follow-up program. However, as reflected in the above-mentioned survey data, the common practice routines outside of clinical studies may diverge dramatically from what is perceived as the clinical standard. The varying practice of vitamin supplementation is further complicated by the availability of a wide array of multivitamin and mineral preparations that differ in their content and composition. Some companies specialize in bariatric vitamin preparations. However, folate and vitamin B₁₂ are not necessarily provided in higher concentrations than in regular multivitamin preparations, which contain moderate doses of folate (200-500 mcg) and low doses of vitamin B₁₂ (6-125 mcg). Also, surprisingly, bariatric multivitamins often lack iron, most likely based on the assumption that iron might be prescribed separately.¹¹⁴ When it is part of a multivitamin formulation, iron rarely exceeds 20 mg per pill based on the recommended daily allowance of elemental iron in menstruating females (15 mg). Given the widespread use of multivitamins by the general population, these restrictions are useful in avoiding iron overload in people at risk, such as in undiagnosed hereditary hemochromatosis, but the resulting doses of iron may be insufficient for bariatric patients.

Even when supplementation is emphasized, patient compliance with long-term vitamin and mineral supplementation is problematic. Brolin et al¹⁵ defined compliance as taking vitamin supplementation ≥5 times per week. Only 33% of patients complied with the recommended supplementation regimen, and 7.7% never took their multivitamin.⁴⁵

Case Study

DM is a 42-year-old premenopausal woman who underwent laparoscopic RYGB in 2004. Her postoperative course was uncomplicated, and at 24 months after her gastric bypass she had lost 70% of her excess weight and her BMI was 29.2 kg/m². Her medical history was significant for iron deficiency anemia. After surgery, her follow-up visits to the bariatric surgery clinic were sporadic. After a 6-month follow-up visit, she was not seen again until her 2-year anniversary. At that visit, she was diagnosed with severe iron deficiency anemia and she admitted to limited compliance with recommended vitamin and mineral supplements. She was counseled and placed on iron supplementation and advised to restart a multivitamin with minerals, calcium citrate, and oral vitamin B₁₂. She had a low serum folate level, confirming that she had not been taking her multivitamin and was placed on folic acid as well. Consideration was given to begin replacement with intravenous iron, but the patient was not seen again for another 18 months because of changes in her insurance coverage. Almost 4 years after surgery, she presented to the bariatric surgery clinic at the direction of her primary care provider, who was uncertain how to proceed with treatment of her severe anemia. Her hemoglobin was 4.3 g/dL and her serum ferritin level was <1 ng/dL. The patient admitted to chest pain, dyspnea on exertion, palpitations, tachycardia, fatigue, exaggerated hair loss, cheilosis, pitting of her nails, and cold intolerance. She carried a cooler filled with ice because she was chewing ice constantly.

Treatment included the administration of 2 units of packed red blood cells. Intravenous iron replacement with iron sucrose was completed over 10 sessions for a total of 2000 mg. The patient took an oral iron supplement with chewable vitamin C after an oral iron absorption test demonstrated that she could adequately absorb iron. It has been difficult to maintain ferritin levels attributable to menorrhagia, and the patient may require further replacement with intravenous iron attributable to her increased losses. See Table 2 for laboratory values.

This case demonstrates the clinical complexities of caring for the bariatric surgery patient. Vitamin and...
Table 2. Case Study: Laboratory Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Presurgery</th>
<th>24 mo</th>
<th>42 mo</th>
<th>44 mo</th>
<th>48 mo</th>
</tr>
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<tbody>
<tr>
<td>Hb, g/dL (12–16 g/dL)</td>
<td>12</td>
<td>6.1</td>
<td>4.3</td>
<td>12.7</td>
<td>12.1</td>
</tr>
<tr>
<td>MCV, fL (82–98 fL)</td>
<td>80</td>
<td>64</td>
<td>60</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>MCH, pg (27–31 pg)</td>
<td>28</td>
<td>18</td>
<td>16</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Serum iron, mcg/dL (28–170 mcg/dL)</td>
<td>724</td>
<td>0.6</td>
<td>&lt;1</td>
<td>22</td>
<td>NA</td>
</tr>
<tr>
<td>Ferritin, ng/mL (20–200 ng/mL)</td>
<td>27</td>
<td>25</td>
<td>&lt;10</td>
<td>114</td>
<td>388</td>
</tr>
<tr>
<td>Folate, ng/mL (≥3 ng/mL)</td>
<td>N/A</td>
<td>1</td>
<td>&lt;1</td>
<td>75</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;, ng/mL (≥220 ng/mL)</td>
<td>434</td>
<td>717</td>
<td>357</td>
<td>NA</td>
<td>366</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular Hb; NA, not available. Values in parentheses are normal ranges.

- Completion of treatment with intravenous iron.
- Maintenance with oral iron.

Conclusions and Recommendations

Anemia following bariatric surgery occurs at a frequency of 30%-60% but was described as high as 74% in early reports. Different types of surgery (eg, bypass vs banding), definitions of anemia, degrees of micronutrient supplementation, and center-dependent policies regarding postsurgical care may account for the variations seen. Iron deficiency is thought to be the most common cause of anemia, although definitions of IDA are often vague and lack inclusion of ferritin as an important diagnostic parameter. Folate and vitamin B<sub>12</sub> deficiencies seem to be rare causes of anemia. Oral vitamin B<sub>12</sub> supplementation, especially at high doses, appears able to overcome absorptive limitations, although mean observation periods of only 2-3 years in most studies may not be sufficient to detect slow depletion of vitamin B<sub>12</sub> stores. Long-term follow-up data in regard to incidence, severity, and causes of anemia are mostly absent. Some authors have indicated that anemia remained undiagnosed in a substantial number of their patients after iron, folate, and vitamin B<sub>12</sub> deficiencies were excluded. Inflammation attributable to obesity as a contributing factor to anemia should be considered in such cases. When dietary iron absorption becomes mechanically limited, as in bariatric patients, persistent inflammation may further aggravate functional iron deficiency. In support of inflammation, the prevalence of anemia in the obese patient prior to surgery is approximately 20% and much higher than would be expected in the normal population.

In addition, the divalent ions copper (when deficient) and zinc (when ingested in large amounts) can interfere with iron uptake in ways that are not completely understood but may lead to anemia. Finally, the relative contributions of vitamins A and E deficiencies to anemia (both fat-soluble and conceivably malabsorbed) after gastric bypass have not been elucidated. Hence, anemia in the bariatric patient may be more complex than previously thought and thus requires thorough evaluation. A frequently encountered challenge in common practice is the distinction between IDA and ACI. The approach outlined in Table 1 may be helpful. In the presence of a low serum iron concentration, ferritin levels <40 ng/dL indicate iron deficiency whereas ferritin levels >200 ng/mL indicate inflammation. Ferritin levels between 40 and 200 ng/dL may represent the combination of IDA and ACI. If the clinician is in doubt, additional measurement of soluble transferrin receptor and its ratio to ferritin will aid in distinguishing between IDA, ACI, or their combination. The distinction is important because ACI will not respond to routine iron supplementation.

Oral iron tolerance tests can be extremely helpful in identifying patients with poor absorption and can facilitate early decision making about the use of intravenous iron. In a normal person, 100-150 mg of elemental iron (2 tablets of iron sulfate) ingested with a small amount of orange juice on an empty stomach will result in a more than 100% increase in serum iron 2-3 hours following ingestion. If test results indicate suboptimal iron absorption, regular administration of intravenous iron should be initiated when ferritin levels are low and inflammation has been ruled out.

Measurement of serum levels of copper, zinc, and vitamins A and E should be considered when the first evaluation of anemia renders no conclusive cause. Referral to a hematologist may be warranted at this point to rule out nonbenign conditions.

Dietary supplementation and frequency of patient follow-up after surgery are at the discretion of the bariatric surgeon. Definitive guidelines are missing, but in
larger bariatric programs, dietitians, and specialized nurse practitioners follow patients regularly regarding the evaluation of nutrition deficiencies. However, a number of patients will not participate in bariatric programs, will not be compliant, and will be lost to follow-up. Those patients will present with symptoms at their community health-care providers, who often are not familiar with the long-term sequelae of bariatric surgery. With this review, we hope to reach those healthcare providers who are closest to the bariatric patient, heighten the awareness for anemia in bariatric surgery, and create the understanding that although iron deficiency may be a prominent cause of anemia in bariatric surgery, and create the understanding that although iron deficiency may be a prominent cause of anemia in this patient population, it does not account for all cases.

References

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