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ORIGINAL CONTRIBUTIONS

Anemia Before and After Roux-en-Y Gastric Bypass: Prevalence and Evolution on Long-Term Follow-up

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Abstract

Purpose Anemia due to iron deficiency or inflammatory state is often associated with obesity. Bariatric surgery is responsible for increasing iron deficiency, but weight loss decreases the inflammatory state associated with obesity. The objective of our study was to investigate the prevalence and causes of anemia before and after bariatric surgery for severe obesity in a 5-year follow-up.

Materials and Methods Retrospective study, with electronic record analysis of obese patients, submitted to Roux-en-Y gastric bypass. Laboratory data were collected before and up to 60 months after surgery. Diagnosis and classification of anemia were done according to hemoglobin levels, serum ferritin, and transferrin saturation.

Results Preoperatively, 8.8% of patients had anemia (93.2%, mild), and 43.8% of the patients had anemia due to chronic disease. After 24 months, there was a progressive increase of iron-deficiency anemia (72.4%) and decrease in anemia due to chronic disease (15.5%) and mixed (12.1%), with maintenance of this profile during long-term follow-up.

Conclusion Anemia is very frequent in severely obese patients and must be investigated both before and after bariatric surgery. The cause of anemia must be determined in order to use the best treatment available. We observed a reduction in the prevalence of chronic disease anemia during long-term follow-up probably due to the improvement in the systemic inflammatory state.

Keywords Obesity · Bariatric surgery · Chronic disease · Anemia

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Introduction

The increasing global prevalence of obesity is considered a pandemic health problem. Severe obesity is associated with chronic systemic diseases such as diabetes mellitus, hypertension, dyslipidemias, and metabolic syndrome [1].

Recent studies have shown that patients with severe obesity have also nutritional deficiencies despite an excessive calorie reserve. The most common micronutritional deficiencies were iron, zinc, vitamin D, and vitamin B12 [2]. Anemia caused by iron deficiency has been described in 5.5–21.9% of severely obese patients before bariatric surgery [3].

In addition to several other causes for these changes, a low-grade chronic inflammatory response associated with obesity and some of its comorbidities contribute to the genesis of anemia in severely obese patients. Activation of the immune system results in pathologic iron homeostasis [3]. This low systemic chronic inflammatory state is associated with several changes in iron homeostasis, erythrocytes production, and lifetime, which contributes to anemia of chronic disease [4].

The elevation of the pro-inflammatory cytokines plays a fundamental role in insulin resistance, inducing the onset of micro- and macrovascular complications, diabetic, cardiovascular and renal, and anemia. The increase of IL-6 mainly results in an anti-erythropoietin effect, due to the alteration of the sensitivity of the erythropoietin progenitor cells (erythroid growth factor), and also promotes apoptosis of immature erythroblasts, causing an even greater reduction in the number of circulating erythrocytes. This mechanisms consequently generate the reduction of circulating hemoglobin. In addition, diabetic and anemic patients have high rates of ultra-sensitive C-reactive protein and ferritin and low serum iron levels, confirming that ferritin elevations were associated with the chronic inflammatory process present in diabetes. The physiopathological mechanisms described above lead to anemia of chronic disease (also called the anemia of inflammation or anemia of chronic inflammation) [5].

The association between obesity and anemia is epidemiologically demonstrated. In the last 30 years, there has been an improvement in the Brazilian and world nutritional patterns, with an increase in the rates of overweight and obesity, a paradoxical persistence of a high incidence of anemia, and even an increase in certain age groups and populations, despite the global decline in protein-calorie malnutrition rates [6].

Nowadays, bariatric surgery is an effective treatment in patients with severe obesity, reducing both comorbidities and mortality. Nevertheless, in spite of effective weight reduction, frequent complications after bariatric surgery are micronutrient deficiencies due to reduced intake and/or absorption [7, 8]. After bariatric surgery, anemia prevalence increases progressively (10–63%), with average annual decreases of 0.5–1% of hemoglobin level [9]. Iron deficiency is considered the most common cause (up to 40%). Nevertheless, it is well known that chronic inflammatory state decreases after weight loss due to bariatric surgery [7].

The aim of our study was to analyze the causes and prevalence of anemia before and after Roux-en-Y gastric bypass (GBP) with a 60-month follow-up in a public tertiary hospital.

Methods

Electronic medical records of 903 patients who underwent GBP between 2006 and 2015 in the Metabolic and Bariatric Unit, Hospital das Clínicas, University of São Paulo Medical School, were retrospectively evaluated. The current study was performed according to the ethical recommendations of the Declaration of Helsinki, and it was approved by the Institution's Ethical Committee. All patients were over 18 years old and had a BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with comorbidities. This group identified and included in the study 831 patients who had preoperative complete laboratory data (hemoglobin, complete iron profile).

The surgical technique was Roux-en-Y gastric bypass. The procedure was realized by the same surgical team and consisted in the creation of a 40-mL gastric pouch with an alimentary limb of 100 cm and 70 cm biliopancreatic limb.

All patients started taking a daily oral multivitamin supplement 1 month after surgery and were instructed to use it continuously, as well as bimontly injections of 1.000 IU of vitamin B12. Reposition of 80 mg of elemental iron (as ferrous sulfate, 200 mg twice daily before meals) was prescribed as required.

Laboratory data were collected before surgery and at the following postoperative intervals: 6–12, 24–36, and 48–60 months after surgery. The diagnosis of anemia was defined as hemoglobin (Hb) level less than 13 g/dL in men and 12 g/dL in women, according to WHO guidelines [10].

Anemia severity was classified as mild (Hb > 10 g/dL), moderate (Hb between 8 and 10 g/dL), and severe (Hb < 8 g/dL). Anemia type was classified according to mean corpuscular volume (MCV) in microcytic (MCV < 80 fL), normocytic (80 < MCV < 100 fL), or macrocytic (MCV > 100 fL) and according to mean corpuscular hemoglobin (MCH) in hypochromic (MCH < 27 pg), normochromic (27 < MCH < 32 pg), or hyperchromic (MCH > 32 pg).

All patients with anemia diagnosis were classified as anemia due to iron deficiency (ID): ferritin level < 40 ng/mL and transferrin saturation (TSAT) < 20%; anemia of chronic disease (CD): ferritin level > 60 mg/mL and TSAT < 40%; and iron deficiency/chronic disease or mixed anemia (MA): ferritin level between 40 and 60 mg/mL and TSAT < 40%.

TSAT was calculated according to the following formula, using serum iron concentration (Fe) and total iron binding capacity (TIBC): [TSAT(%) = (Fe/TIBC) × 100] [3].

Results

The mean age was 47 ± 12 years old and 81% were women. The mean BMI was 46.5 ± 3.2 kg/m^2. There was no significant difference in clinical characteristics between patients with and without anemia (Table 1).

Table 1 Preoperative data of the group showing no differences between patients with and without anemia ($n = 831$)

	Normal (%)	Anemia (%)
Gender		
Female	678 (81.1)	87 (79.1)
Male	158 (18.8)	23 (20.9)
Age (years)	42 ± 12	41.5 ± 11
BMI (kg/m^2)	45.1 ± 3	44.8 ± 2.9
Super obese	30	29

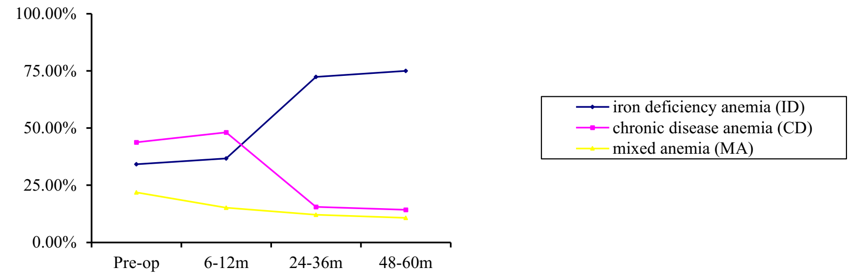

Fig. 1 Graphic representation of the prevalence of the causes of anemia during postoperative follow-up

From 831 patients, 8.8% (73) had anemia (93.2%, mild) before surgery. The chronic disease (CD) anemia was the most frequent cause, being observed in 43.8% of patients. Another 34.3% had anemia related to iron deficiency (ID), and 21.9% presented mixed anemia (MA) (Table 1).

At 12 months follow-up, anemia distribution was stable (48.1% CD, 36.7% ID, and 15.2% MA), with 87% of cases been mild anemia.

After 24 months, we observed a great decrease of CD anemia (15.5%) and MA (12.1%) and an increment of ID anemia (72.4%). At the long-term follow-up (48–60 months), ID anemia remained the most prevalent (75%) followed by CD anemia (14.3%) and MA (10.7%) (Table 2) (Fig. 1). At this time of follow-up, 53.6% (62) of patients had mild and 46.4% had moderate anemia.

The analysis of the MCV and MCH profiles according to anemia classification is shown in Table 3. Hematimetric indexes were not useful in classifying anemia in patients with severe obesity [11].

Discussion

Chronic low inflammatory state is associated with severe obesity. The adipose tissue has been recognized as metabolic active with the release of pro-inflammatory cytokines [12]. This chronic inflammatory state explains the high incidence of preoperative CD anemia (Table 2). In our study, with the predominance of women, the also elevated prevalence of iron-deficiency anemia before surgery can be associated both to nutritional deficiency and blood loss from menstruation. Nonetheless, insufficient compensation of blood losses because of inadequate iron intake, not uncommon in patients that are chronically under reduced energy diets trying a clinical treatment of obesity, could also play a role in female participants with anemia. On the other hand, mobilization of iron stores and impaired iron absorption resulting from the inflammatory state associated with obesity has been linked to iron deficiency in these patients and also plays a major role in the pathophysiology of anemia in these patients [13].

After bariatric surgery, in our series, chronic disease and iron deficiency continued as the major causes of anemia, with more occurrence of mild normocytic/normochromic disease (Tables 2 and 3). Nonetheless, throughout the follow-up, with weight loss, we observe a change in the anemia type, with expressive decreasing in CD anemia and progressive increase of ID anemia. Until the first year of postoperative, probably an inflammatory state linked to severe weight loss (a major part of total weight loss occurs in the first 6 months after surgery) is sufficient to maintain the high incidence of CD anemia. But after 1 year, the CD anemia lowers drastically, following a deceleration in weight loss, and improvement in comorbidities, also a cause of CD anemia, like type 2 diabetes.

Recent studies showed inflammation decrease is associated with weight loss [14]. The decrease in chronic inflammation as well as the improvement of comorbidities could explain this change in the pattern of anemia with progressive weight loss.

Table 2 Prevalence of anemia over postoperative time and its distribution classified by severity and cause

	Preop, % (*n*) (*N* = 831)	6–12 months, % (*n*) (*N* = 431)	24–36 months, % (*n*) (*N* = 221)	48–60 months, % (*n*) (*N* = 116)
Anemia	8.8 (73)	18.3 (79)	26.2 (58)	24.1 (28)
Mild	93.2 (68)	87.4 (69)	67.3 (39)	53.6 (15)
Moderate	6.8(5)	10.1 (8)	17.2 (10)	46.4 (13)
Severe	–	2.5 (2)	15.5 (9)	–
Iron deficiency	34.3 (25)	36.7 (29)	72.4 (42)	75.0 (21)
Chronic disease	43.8 (32)	48.1 (38)	15.5 (9)	14.3 (4)
Mixed anemia	21.9 (16)	15.2 (12)	12.1 (7)	10.7 (3)

Table 3 Classification of anemia according to MCV and MCH

	Iron deficiency ID (%)		Chronic disease CD (%)		Mixed MA (%)	
	normo/normo	micro/hipo	normo/normo	micro/hipo	normo/normo	micro/hipo
Preop	44.0	56.0	69.0	28.0	81.0	19.0
6–12 months	58.0	41.0	84.0	13.0	91.0	8.0
24–36 months	38.0	61.0	77.0	11.0	57.0	43.0
48–60 months	38.0	62.0	–	75.0	100.0	–

A decrease in iron stores mobilization once caused by a chronic inflammatory state, and improvement of iron absorption capacity secondary to lower levels of circulating hepcidin and other acute phase proteins, could compensate the impairment of intestinal iron absorption caused by duodenal and initial jejunum bypass of Roux-en-Y in GBP [5, 13].

After surgery, the progressive increase in the incidence of ID anemia is compatible with the literature data. The reported incidence of postoperative ID anemia after bariatric surgery ranges from 12 to 47% [7, 8, 12–15]. In our study, 441 (53.1%) of the 831 patients included were iron deficient (Table 3).

It largely occurs as a result of postoperative inadequate dietary intake, diminished absorption caused by the postoperative changes in the digestive tract, and physiologic or pathologic losses.

Iron deficiency was more common in women, particularly those who were premenopausal or had a history of abnormal uterine bleeding. With prophylactic supplementation of oral iron, iron deficiency can be prevented, but it did not consistently protect menstruating women after gastric bypass from developing anemia. Nonetheless, a significative number of obese women have amenorrhea. With postoperative weight loss and menstrual cycle normalization, a new postoperative source of iron loss and consequently ferritin depletion is expected [3, 14].

Most of the morbidly obese women with irregular menstrual patterns regain normal cycles after bariatric surgery [7]. It is possible that the normalization of menses may increase the risk of developing iron deficiency after GBP. However, menstrual bleeding alone does not explain the high incidence of ID anemia. Food aversions, the most common are secondary to intolerance to red meat and other high-protein foods, and modified dietary behaviors can also lead to a low intake of sources of iron.

Malabsorption also plays a major role in the pathophysiology of iron deficiency in patients after GBP. Reduction of iron (III) to iron (II) is strongly dependent on the presence of gastric acid. GBP decreases gastric acid secretion in the pouch, impairing substantially gastric acidity. This, in turn, decreases the availability of the reduced form of iron [3]. Most of the iron absorption occurs in the duodenal enterocytes. However, after GBP, the duodenum is excluded from digestive continuity, further impairing iron absorption, even with the improvement in iron absorption by distal enterocytes [8, 16].

Iron deficiency may occur also as a result of blood loss caused by operative complications, as in case of marginal ulcers, ulcers, and other lesions in other segments of the small bowel, duodenum, or excluded stomach. Some patients may also experience postoperative iron-losing enteropathy [17].

Another important factor for increasing iron-deficiency anemia after GBP is the difficulty of oral iron supplementation. Iron present in multivitamins has low bioavailability after GBP (commonly as ferrous sulfate), and iron-specific supplementation, or reposition in case of deficiency, through compounds with better postoperative absorption, such as iron chelated formulations, has high cost, and yet gastrointestinal side effects make the maintenance of its use difficult. Non-compliance with iron supplementation may also increase ID anemia. On the other hand, parenteral supplementation requires multiple endovenous applications in the case of iron sucrose, or it has a high cost in the case of more modern compounds, such as iron maltose. Regardless, parenteral supplementation therapy is often the best option in case of recurrent or more severe anemia [18].

Conclusion

In conclusion, the prevalence of anemia due to chronic disease is very reduced on long-term follow-up after bariatric surgery, probably due to the inflammatory status improvement.

Compliance with Ethical Standards

Conflict of Interest Roberto de Cleva, Lilian Cardia, Daniel Riccioppo, Miwa Kawamoto, Newton Kanashiro, and Marco Aurelio Santo have no conflict of interest.

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards."

Informed Consent Statement Does not apply.

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