OBES SURG (2017) 27:1993–1999
DOI 10.1007/s11695-017-2582-0

ORIGINAL CONTRIBUTIONS

Status of Iron Metabolism 10 Years After Roux-En-Y Gastric Bypass

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Published online: 14 February 2017

Abstract
Background The aim of this study is to investigate changes in iron metabolism and verify whether biochemical parameters are related to the use of oral iron supplement 10 years after Roux-en-Y gastric bypass.
Methods This longitudinal retrospective study included 151 patients submitted to Roux-en-Y gastric bypass. The collected data included use of an oral iron supplement, hemoglobin, hematocrit, serum iron, and ferritin. The chi-squared or Fisher's exact test was used to analyze the association between use of iron supplement and nutritional deficiency. The generalized estimating equations (GEEs) analyzed the nutritional deficiencies over time.
Results Of the study patients with iron-deficiency anemia (n = 15) in the 12-month follow-up, 73.33% (n = 11) were taking an iron supplement, and 26.67% (n = 4) were not (p = 0.0010). The effect of time was significant for hemoglobin, ferritin, iron overload (p < 0.0001), and hematocrit (p = 0.0007). Of the patients who remained in the study until the 120-month follow-up, 37.5 and 45.0% were diagnosed with iron-deficiency anemia, defined as ferritin <15 μg/L and ferritin <30 μg/L, respectively.
Conclusions Iron-deficiency anemia increased over time even in patients taking oral iron supplements.

Keywords Gastric bypass · Iron deficiency · Iron-deficiency anemia · Oral iron supplement

Introduction

Even with the growing increase of vertical gastrectomy in the USA and Canada, Roux-en-Y gastric bypass is still the most common bariatric surgery in Latin America [1]. It is a safe and effective procedure for morbidly obese patients [2]. Ten years after surgery, patients have approximately 70% less of their excess weight [3] and 80% of the patients no longer have diabetes mellitus [3]. Nonetheless, nutritional deficiencies may occur [4] as a consequence of the restrictive effects of surgery associated with the changes in nutrient absorption [5], which require proper nutritional management.

Roux-en-Y gastric bypass patients may present changes in iron metabolism and anemia [4–7], highly prevalent after surgery [5, 6], requiring careful treatment especially in young women of childbearing age [5, 7].

Iron-deficiency anemia after bariatric procedures is frequent [6–8]. It is associated with certain risk factors, such as food intolerance, malabsorption, hypochloridria, duodenal and proximal jejunal bypass, and menstrual losses stemming from hormonal changes secondary to adipose tissue loss [5, 7, 9].

Clinical and nutritional monitoring with an iron supplementation program [5], monitoring of biochemical parameters [10], and clinical strategies to control menstrual losses in women [7] are important for the care of bariatric surgery patients with iron deficiency and anemia [5, 7, 9, 10].

Article based on the master's dissertation of Daniela Vicinansa Monaco-Ferreira

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In 2015, Karefylakis et al. [11] found that 27% of the patients in the 10-year follow-up were anemic, but anemia was less common in patients who had had biochemical tests regularly [11].

Iron supplementation is essential for gastric bypass patients [5–8]. Yet, oral iron supplement absorption may be compromised because of the possibly limited effects of oral tablets [8].

Considering the importance of iron metabolism before and after surgery, the objective of this study was to investigate changes in iron metabolism and relate biochemical parameters with the use of oral iron supplements by patients 10 years after Roux-en-Y gastric bypass.

Casuistic and Method

Study Design

This retrospective, longitudinal study conducted at a multidisciplinary center for the treatment of obesity collected data from the medical and nutritional records of patients submitted to Roux-en-Y gastric bypass. The study patients underwent gastric bypass between January 2005 and May 2015, a follow-up period of 10 years. The inclusion criteria were having undergone unbanded laparoscopic Roux-en-Y gastric bypass, and regular medical and nutritional follow-up in the first year after surgery. The study excluded patients submitted to other surgical techniques or those who did not attend the medical and nutritional follow-ups in the first year after surgery. Thus, the study included 151 patients based on preoperative data. This study is part of a greater master's program project, approved by the local Research Ethics Committee (protocol no. 1.132.168).

Data Collection

Use of an oral iron supplement and hemoglobin, hematocrit, serum iron, and ferritin test results were collected from the patients' medical and nutritional records. These variables were collected preoperatively and 3, 6, 12, 24, 48, 72, 96, and 120 months after surgery.

Use of Iron Supplement

Oral iron supplement use was classified as *YES* for those who took it and *NO* for those who did not. The patients were advised by the multidisciplinary team to use chelated iron supplements.

Biochemical Tests

The biochemical tests included hemoglobin, hematocrit, serum iron, and ferritin. All data were recorded thoroughly before and 3, 6, 12, 24, 48, 72, 96, and 120 months after surgery.

Anemia was defined as recommended by the World Health Organization (WHO) in 2011 [12] as follows: hemoglobin <12 g/L for women and <13 g/L for men [12]. Iron-deficiency anemia was defined as ferritin <15 μg/L, as recommended by the WHO in 2011 [13]. However, iron-deficiency anemia defined as ferritin <30 μg/L [14] was also investigated, as proposed by Short and Domagalski [14], to improve diagnostic sensitivity and specificity. Serum iron deficiency was defined as serum iron <65 μg/dL for women and <75 μg/dL for men [15]. Low hematocrit was defined as <36% for women and <39% for men [16]. Iron overload was diagnosed as recommended by the WHO in 2011 [13] as follows: ferritin >150 μg/L for women and >200 μg/L for men.

Statistical Analysis

The data were tabulated in Microsoft Excel®, and the statistical analyses were performed by the software SAS [17]. The nominal variables were expressed as percentages. The chi-squared test or the Fisher's exact test when appropriate compared the proportions of patients with and without nutritional deficiencies, who took or not oral iron supplements [18]. The generalized estimating equations (GEEs) compared proportions over time [19]. The significance level was set at 5%.

Results

Figure 1 and Table 1 show the results for iron metabolism. Before surgery, most patients had normal hemoglobin and hematocrit, but 23.5% of the patients had iron deficiency, and 2.99% had iron-deficiency anemia defined as ferritin <15 μg/L (Table 1). Twelve months after surgery, 18.32% of the patients had anemia and 11.63% had iron-deficiency anemia defined as ferritin <15 μg/L (Table 1).

In the 72-, 96-, and 120-month follow-ups, 22.86%, 21.15, and 21.43% of the patients, respectively, had anemia based on their hemoglobin levels (Table 1).

In the 72-, 96-, and 120-month follow-ups, 20.63, 20.93, and 20.59% of the patients, respectively, had low hematocrit (Table 1).

In the 72-, 96-, and 120-month follow-ups, 17.14, 25.0, and 20.5 of the patients, respectively, had iron deficiency (Table 1).

In the 72-, 96-, and 120-month follow-ups, 29.85, 26.09, and 37.5% of the patients, respectively, had iron-deficiency anemia defined as ferritin <15 μg/L (Table 1).

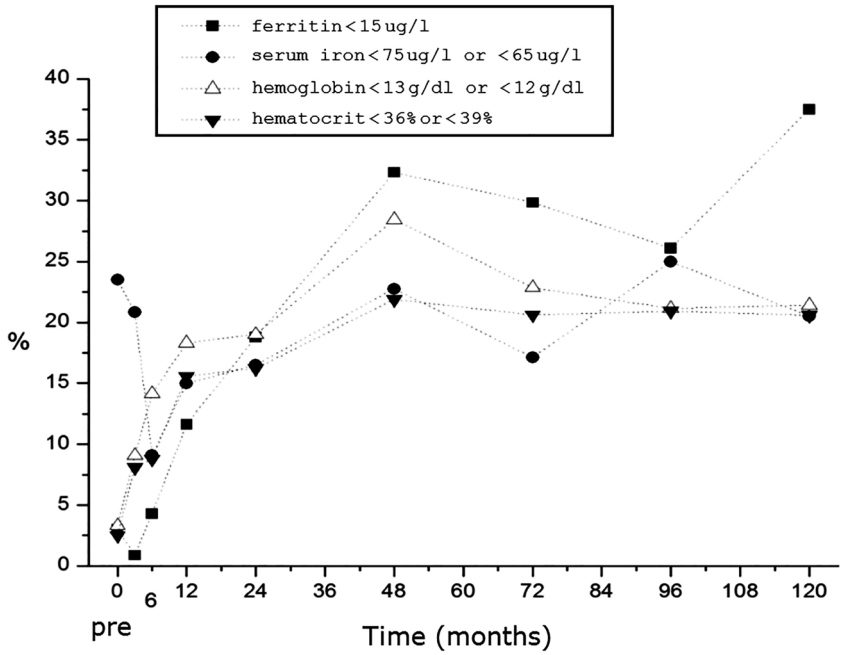

Fig. 1 Prevalence over time of nutritional deficiencies related to iron metabolism according to the generalized estimating equations (GEEs)

According to the GEE, the effect of time was significant for the nutritional deficiencies related to hemoglobin, ferritin <15 μg/L, ferritin <30 μg/L, iron overload ($p < 0.0001$), and hematocrit ($p = 0.0007$) (Fig. 1 and Table 1).

Table 1 Prevalence of nutritional deficiencies related to iron metabolism 10 years after Roux-en-Y gastric bypass

Time/tests	Preoperative		3 months		6 months		12 months		24 months		48 months		72 months		96 months		120 months	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Hemoglobin[c] ($p < 0.0001$)																		
Adequate	146	96.69	110	90.91	79	85.87	107	81.68	98	80.99	73	71.57	54	77.14	41	78.85	33	78.57
Deficient	5	3.31	11	9.09	13	14.13	24	18.32	23	19.01	29	28.43	16	22.86	11	21.15	9	21.43
Hematocrit[c] ($p = 0.0007$)																		
Adequate	120	97.5	102	91.89	83	91.21	103	84.43	93	83.78	75	78.13	50	79.37	34	79.07	27	79.41
Deficient	3	2.50	9	8.11	8	8.79	19	15.57	18	16.22	21	21.88	13	20.63	9	20.93	7	20.59
Serum iron[c] ($p = 0.2190$)																		
Adequate	104	76.47	95	79.17	80	90.91	108	85.04	96	83.48	78	77.23	58	82.86	36	75.00	31	79.49
Deficient	32	23.53	25	20.83	8	9.09	19	14.96	19	16.52	23	22.77	12	17.14	12	25.00	8	20.51
Ferritin[a,c] ($p < 0.0001$)																		
Adequate	130	97.01	113	99.12	89	95.7	114	88.37	95	81.2	67	67.68	47	70.15	34	73.91	25	62.5
Deficient	4	2.99	1	0.88	4	4.30	15	11.63	22	18.8	32	32.32	20	29.85	12	26.09	15	37.5
Ferritin[b,c] ($p < 0.0001$)																		
Adequate	122	91.04	100	87.72	81	87.10	99	76.74	74	63.25	48	48.48	30	44.78	21	45.65	22	55.0
Deficient	12	8.96	14	12.28	12	12.9	30	23.36	43	36.75	51	51.52	37	55.22	25	54.35	18	45.0
Iron overload[c] ($p < 0.0001$)																		
Normal	93	69.4	74	64.91	67	72.04	103	79.84	96	82.05	87	87.88	62	92.54	45	97.83	34	85.0
High	41	30.6	40	35.09	26	27.96	26	20.16	21	17.95	12	12.12	5	7.46	1	2.17	6	15.0

Time follow-up time in months, *Preop*. preoperative

[a] Ferritin, <15 μg/L

[b] Ferritin, <30 μg/L

[c] Generalized estimating equations (GEEs), using a significance level of 5%

In the 72-, 96-, and 120-month follow-ups, 55.22, 54.35, and 45.0% of the patients, respectively, had iron-deficiency anemia defined as ferritin <30 μg/l ($p < 0.0001$) on all study occasions (Table 1).

Iron overload was found in 30.6% of the patients before surgery, based on the reference values provided by the WHO in 2011 [13]. In the 72-, 96-, and 120-month follow-ups, 7.46, 2.17, and 15.0% of the patients, respectively, had iron overload ($p < 0.0001$) (Table 1).

In the 12-month follow-up, 50 patients (32.5%) were taking oral iron supplements; in the 24-month follow-up, 45 patients (31.5%); in the 48-month follow-up, 40 patients (34.5%); in the 72-month follow-up, 28 patients (34.6%); in the 96-month follow-up, 16 patients (26.7%); and in the 120-month follow-up, 19 patients (44.2%) (data not tabulated).

Tables 2 and 3 show the association of oral iron supplement use with iron-deficiency anemia defined as ferritin <15 μg/L and anemia based on hemoglobin level.

Of the study patients with iron-deficiency anemia ($n = 15$) in the 12-month follow-up, 73.33% ($n = 11$) were taking an iron supplement and 26.67% ($n = 4$) were not ($p = 0.0010$). The same occurred in the 48- and 72-month follow-ups, 62.5% ($n = 32$) and 60% ($n = 20$) of the patients, respectively, were taking an iron supplement (Table 2).

Table 3 shows that 52.17 and 47.83% of the study patients with anemia ($n = 23$) were and were not, respectively, taking an iron supplement in the 12-month follow-up ($p = 0.0406$). The same occurred in the 24-month follow-up: 56.52% ($n = 23$) and 43.48% of the patients with anemia were and were not, respectively, taking an iron supplement ($p = 0.0119$).

Discussion

The present study found that 3.31 and 18.32% of the patients were diagnosed with anemia before and 12 months after surgery, respectively, based on hemoglobin level. The prevalence of anemia after surgery increased over time. Salgado et al. [7] found that 21.5% of a public healthcare service users in Brazil had anemia before surgery, and the number of patients with anemia did not change in the 4-year study period, but ferritin decreased considerably over time. Many studies have found anemia in patients before they underwent Roux-en-Y gastric bypass [7, 20, 21]. Obinwanne et al. [22], assessed the incidence of iron deficiency, its results, and treatment 10 years after Roux-en-Y gastric bypass. Their results were similar to those of the present study with respect to the study population, criteria used, and results [22].

Karefilysis et al. [11] found a 27% prevalence of anemia 10 years after gastric bypass, but anemia did not worsen over time and was less frequent in patients submitted to biochemical tests. In the present study, analyses of the effect of time found that all study parameters differed significantly over time.

A recent systematic review and meta-analysis [9] about anemia after Roux-en-Y gastric bypass [9] found anemia in the 12-month follow-up and that hemoglobin and hematocrit decrease considerably over time. The present study also found that hemoglobin, hematocrit, and ferritin decrease over time, differing significantly between study occasions. Similar results were reported by Salgado et al. [7], in a 4-year follow-up, and by Weng et al. [9], in a meta-analysis; both studies reported that ferritin tended to decrease, being worse in the 24-

Table 2 Association between the use of an oral iron supplement and iron-deficiency anemia, defined as ferritin <15 μg/L, 10 years after Roux-en-Y gastric bypass

Follow-up time	Iron-deficiency anemia					No iron-deficiency anemia						
		Supplement No		Supplement Yes			Supplement No		Supplement Yes		*p* value	*N* total
	N	*N*	%	*N*	%	*N*	*N*	%	*N*	%		
3 months	1	1	100	–	–	113	69	61.06	44	38.94	–	114
6 months	4	1	25.0	3	75.0	89	56	62.92	33	37.08	0.2949[b]	93
12 months	15	4	26.87	11	73.33	113	79	69.91	34	30.09	0.0010[a]	128
24 months	22	13	59.09	9	40.91	94	61	64.89	33	35.11	0.6102[a]	116
48 months	32	12	37.5	20	62.5	67	53	79.10	14	20.9	0.0001[a]	99
72 months	20	8	40.0	12	60.0	46	33	71.74	13	28.26	0.0146[a]	66
96 months	12	8	66.67	4	33.33	34	26	76.47	8	23.53	0.7034[b]	46
120 months	14	5	35.71	9	64.29	25	16	64.0	9	36.0	0.0892[a]	39

Follow-up time in months. Values expressed as number of cases and percentage. Biochemical test of serum ferritin <15 μg/L for comparative analysis

[a] Chi-squared test

[b] Fisher's exact test

Table 3 Association between the use of an oral iron supplement and anemia, defined according to hemoglobin criteria, 10 years after Roux-en-Y gastric bypass

Follow-up time	Iron-deficiency anemia					No iron-deficiency anemia					*p* value	*N* total
		Supplement No		Supplement Yes			Supplement No		Supplement Yes			
	N	*N*	%	*N*	%	*N*	*N*	%	*N*	%		
3 months	11	4	36.36	7	63.64	110	71	64.55	39	35.45	0.1011[b]	121
6 months	13	6	46.15	7	53.85	79	48	60.76	31	39.24	0.3216[a]	92
12 months	23	11	47.83	12	52.17	107	75	70.09	32	29.91	0.0406[a]	130
24 months	23	10	43.48	13	56.52	97	69	71.13	28	28.87	0.0119[a]	120
48 months	29	15	51.72	14	48.28	73	49	67.12	24	32.88	0.1468[a]	102
72 months	16	8	50.0	8	50.0	51	35	68.63	16	31.37	0.1752[a]	67
96 months	11	7	63.64	4	36.36	41	29	70.73	12	29.27	0.7195[b]	52
120 months	9	4	4.44	5	55.56	32	19	59.38	13	40.63	0.4710[b]	41

Follow-up time in months. Values expressed as number of cases and percentage. Biochemical test of hemoglobin for comparative analysis

[a] Chi-squared test

[b] Fisher's exact test

and 36-month follow-ups. The ferritin levels of the study sample were lowest in the 24-, 48-, and 72-month follow-ups but had increased some by the 120-month follow-up.

Assessing the prevalences of iron-deficiency anemia and iron-deficiency over time, on multiple occasions as done by the present study, has become useful and important for deficiency analyses as it was possible to identify when deficiencies occur and establish prevalences on specific occasions after surgery. However, the present study shows the difficulties associated with following this population. The number of assessed patients differed in the 10-year follow-up. Not all patients had complete medical records due to losses to follow-up and biochemical test adherence. In the 10-year follow-up, 27.8% (42) and 29.85% (40) of the patients had the data that enabled the diagnosis of anemia based on hemoglobin and ferritin, respectively.

Kotkiewicz et al. [23] assessed anemia and the need of intravenous iron supplementation after gastric bypass and found that few studies conducted a 10-year follow-up, making this a strength of the present study.

According to bariatric surgery guidelines [10], patients should undergo routine tests at least once a year to monitor hemoglobin, serum iron, and ferritin.

A recent study that assessed dietary pattern and intake of dietary iron sources 4 years after Roux-en-Y gastric bypass found that intolerance to red meat was frequent, which can be related to iron intake [24]. Oral iron supplementation is necessary after gastric bypass [5–8], and iron-deficiency anemia often cannot be prevented with a standard multivitamin, requiring instead a chelated iron supplement, and in more severe anemia, parenteral iron replacement therapy [22, 23].

The present study investigated self-reported adherence to the prescribed iron supplement after surgery, and its relationship with anemia and iron-deficiency anemia. Oral iron supplements did not always protect the patients from anemia and depletion of iron reserves. The causes for iron deficiency and iron-deficiency anemia are multifactorial and involve not only low iron absorption because of the restrictive nature of the surgery but also because of menstrual losses, lower intake of dietary iron sources, and variable adherence to iron supplementation. Once iron-deficiency anemia is diagnosed, the dosage of iron chelate associated with vitamin C must be adjusted accordingly, but if supplementation is inefficient, intravenous replacement under medical supervision is necessary [8, 23].

Patients need to be informed about the metabolic consequences of not adhering to the postoperative treatment. The health professionals who follow these patients must watch the clinical signs carefully to diagnose iron-deficiency anemia in a timely manner and use biochemical tests regularly to monitor the patients' serum iron levels [10].

James et al. [25] assessed self-reported adherence to micronutrient supplements after Roux-en-Y gastric bypass and found excellent adherence to a standard multivitamin/multimineral supplement and a smaller prevalence of nutritional deficiencies.

Blume et al. [26] assessed supplement use in a healthcare facility in the Brazilian South and found that 72.4% of the patients were still taking the supplement 36 months after surgery. Almost half (44.2%) of the study patients were taking the iron supplement 120 months after surgery, but the supplement did not protect them from long-term iron deficiency.

A recent Brazilian study about weight regain [27] found a relationship between weight regain and iron deficiency. Similar results were described by Cambi et al. [28].

Conclusion

In the 10-year follow-up, iron-deficiency anemia was found in approximately 50% of the study population. Iron-deficiency anemia increased over time, and oral iron supplements were not capable of protecting the patients from the condition. These findings confirm the importance of paying attention to the iron metabolism of patients submitted to Roux-en-Y gastric bypass.

Study Limitations

The study limitations include the study design and the patients lost to follow-up, which occurs frequently in this population. The retrospective character of the study prevented the assessment of other variables that could help justify the nutritional outcomes.

Acknowledgments We thank the Pontifical Catholic University of Campinas-SP-Brazil and the Coordination for the Improvement of Higher-education Personnel for the master's scholarship provided to the Master's Program in Health Sciences of Puc-Campinas-SP-Brazil.

Compliance with Ethical Standards

Statement of Authorship DVMF conceived and designed the study, collected and analyzed data, and wrote the manuscript. VALM helped to conceive the study, supervised the research, and reviewed the manuscript. The authors read and approved the final version of the article.

Sponsor This project was not sponsored.

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval 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 Does not apply. For this type of study formal consent is not required.

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