



Original/*Obesidad*

Ferritin in hypertensive and diabetic women before and after bariatric surgery

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Abstract

In addition to its important role as marker of iron stores, serum ferritin is a marker of systemic inflammation, and obesity has been associated with chronic inflammation.

Objective: To verify, six months after surgery, the effect of bariatric surgery on the serum ferritin of women who were hypertensive, diabetic, or comorbidity free before surgery.

Sample and methods: This retrospective study included 200 women aged 20 to 45 years, with a body mass index (BMI) equal to or greater than 35 kg/m², submitted to Roux-en-Y gastric bypass (RYGB). Seventy of these women were hypertensive, forty had type 2 diabetes (T2D), and ninety were comorbidity free (CF). They were assessed before and six months after surgery. Anthropometric, laboratory (serum ferritin and hemoglobin), and comorbidity-related data were collected from their medical records.

Results: Before surgery, women with comorbidities were older, the hypertensives had higher BMI, and the diabetics had higher serum ferritin levels than the CF women. The study comorbidities had resolved in 68% of the hypertensive women and 86% of the diabetic women six months after RYGB. Also at this time, the serum ferritin of hypertensive women decreased from 110.1±86.3 to 88.7±80.5 ng/dL and of diabetic women, from 164.8±133.4 to 101.2±97.7 ng/dL (*p*<0.05); hemoglobin also decreased in hypertensive and CF women (*p*>0.05).

Conclusion: High ferritin in premenopausal obese women was associated with the main obesity-related comorbidities, and these comorbidities determined the reduction of serum ferritin after bariatric surgery.

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Key words: Ferritin. Inflammation. Obesity. Comorbidities. Bariatric surgery.

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LA FERRITINA EN MUJERES HIPERTENSAS Y DIABÉTICAS ANTES Y DESPUÉS DE LA CIRUGÍA BARIÁTRICA

Resumen

Además de importante marcador de las reservas de hierro, la ferritina sérica es un marcador de la inflamación sistémica, mientras que la obesidad se ha asociado con la inflamación crónica.

Objetivo: Identificar, después de 6 meses, el efecto de la cirugía bariátrica sobre los niveles de ferritina sérica en hipertensos, diabéticos o sin estas comorbilidades preoperatorias mujeres.

Pacientes y métodos: Los autores realizaron un estudio retrospectivo de 200 mujeres sometidas a bypass gástrico en Y de Roux (BGYR), con edades comprendidas entre 20 y 45 años, con un índice de masa corporal (IMC) superior a 35 kg/m², con hipertensión arterial (HA, n = 70), la diabetes mellitus tipo 2 (DM2, n = 40) y sin comorbilidades (SC, n = 90) fueron evaluados antes y 6 meses después de BGYR. Antropométricas, de laboratorio (ferritina sérica y hemoglobina) y la información de comorbilidad se recogió de la historia clínica electrónica.

Resultados: Antes de la cirugía, las mujeres con comorbilidades eran mayores, tenían mayores hipertensos IMC, niveles más altos de ferritina diabéticos en relación con el grupo SC. La resolución de las comorbilidades después de 6 meses de DGYR ocurrió en el 68 % de las mujeres con hipertensión y el 86 % de los diabéticos. 6 meses después de la cirugía, se observó una disminución de la ferritina sérica en mujeres con comorbilidades de 110,1 ± 86,3 a 88,7 ± 80,5 ng/dl en el grupo con hipertensión y 164,8 ± 133,4 a 101,2 ± 97,7 ng/dl en DM2 (*p* < 0,05) y la hemoglobina, excepto en los pacientes diabéticos (*p* > 0,05).

Conclusión: El aumento de la ferritina en mujeres obesas en el periodo de premenopausa se relacionan con las principales comorbilidades de la obesidad, y la presencia de estas comorbilidades fue fundamental en la reducción de la ferritina sérica después de la cirugía bariátrica.

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Palabras clave: La ferritina. Inflamación. La obesidad. Comorbilidades. La cirugía bariátrica.

Abbreviations

BMI: Body mass index.

RYGB: Roux-en-Y gastric bypass.

T2D: Type 2 diabetes.

CF: Comorbidity free.

%EWL: Percentage excess weight loss.

WHO: World Health Organization.

ANOVA: Analysis of variance.

Introduction

Obesity is currently an important cause of mortality because it increases the risk of comorbidities considerably, such as hypertension and type 2 diabetes (T2D). Low-grade chronic inflammation is usually associated with obesity and its related comorbidities^{1,2}. Studies have established a strong relationship between adiposity, inflammation, insulin resistance, and high ferritin^{3,4,5,6,7}. Serum ferritin can be a marker of iron store but is also an inflammatory biomarker^{6,7}.

The metabolic syndrome, particularly T2D, help to increase ferritin in obese individuals⁸. A recent meta-analysis considered serum ferritin an independent factor positively associated with the metabolic syndrome and its components⁹. In morbidly obese individuals, ferritin may indicate a new phenotype of insulin resistance^{10,11}.

Obese women experience high ferritin, high hepcidin, and low serum iron accompanied by high hemoglobin, some of the changes associated with anemia of inflammation^{2,3,4,12}. On the other hand, iron-deficiency anemia occurs frequently in women after bariatric surgery.

Iron stores after bariatric surgery are often determined by serum ferritin, which tends to decrease over time and is associated with the iron-deficiency anemia caused by the anatomic and physiological changes promoted by the surgery, such as the higher blood losses that occur postoperatively in women of childbearing age^{13,14,15,16,17}. However, studies on this subject have not investigated how comorbidities contribute to high serum ferritin and the impact of surgery on its status.

Thus, we propose the hypothesis that the inflammatory process associated with obesity increases serum ferritin and that obesity-related comorbidities increase it further, so its decrease should vary after surgery. Hence, this study aimed to verify the effect of bariatric surgery on the serum ferritin of women with or without preoperative hypertension and/or diabetes six months after bariatric surgery.

Sample and methods

This is a retrospective study of 200 comorbidity-free (CF), diabetic, and/or hypertensive premenopausal women examined before (baseline) and six months after (endline) surgery, aged 20 to 45 years, with a baseline body mass index (BMI) of 35 kg/m² or more, submit-

ted to Roux-en-Y gastric bypass (RYGB) between August 2011 and June 2013. The women were recruited at the Bariatric Clinic of the Hospital dos Fonecedores de Cana in Piracicaba-SP, Brazil. This was a convenience sample: all women who underwent RYGB, met the inclusion criteria during the study period, and were reexamined at endline were included. The following baseline and endline information was collected from their electronic medical records: age, height, weight, laboratory test results (serum ferritin and hemoglobin), associated diseases, and use of medications.

Baseline BMI was calculated by dividing the baseline weight in kilograms by the square of the height in meters (kg/m²), and endline percentage of excess weight loss (%EWL) by multiplying the weight lost by 100 and dividing by the excess weight. Excess weight was given by subtracting the ideal weight from the baseline weight¹⁸.

The patient was considered anemic when hemoglobin was below 12 g/dL, a cutoff point established by the World Health Organization (WHO) in 2001¹⁹ which takes age and sex into account. The reference range used for serum ferritin was 15 to 150 ng/mL. The patient was considered iron deficient when serum ferritin was below 15 ng/mL, and at high risk of iron overload when serum ferritin exceeded 150 ng/dL²⁰. Serum ferritin was also analyzed as recommended by Weiss and Goodnough (2005)²¹, who differentiated iron-deficiency anemia from anemia of inflammation as follows: iron-deficiency anemia when ferritin < 30 ng/mL; anemia of inflammation associated with iron-deficiency anemia when 30 ng/mL ≤ ferritin ≤ 100 ng/mL; and anemia of inflammation when ferritin > 100 ng/mL. The baseline serum ferritin and hemoglobin levels were measured immediately before surgery, and hemoglobin levels < 10 g/dL were corrected before surgery.

Hypertension and T2D were considered resolved when the patients no longer required any of the medications they were taking at baseline. Patients with baseline hypertension and T2D were included in the T2D group.

The hypertensive (n=70), diabetic (n=40), and comorbidity-free (n=90) women were compared with respect to age, baseline BMI, %EWL, and baseline and endline serum ferritin and hemoglobin.

This study is part of the project “*Nutrição, obesidade mórbida e cirurgia bariátrica: fatores de suscetibilidade e estudo prospectivo de aspectos genéticos, dietéticos e metabólicos*” (Nutrition, morbid obesity, and bariatric surgery: susceptibility factors and prospective study of the genetic, dietetic, and metabolic aspects) approved by the Research Ethics Committee of Botucatu’s School of Medicine of Universidade Estadual Paulista “Júlio de Mesquita Filho,” under protocol number 3303-2009. All patients met one of the international criteria for indication of bariatric surgery: BMI of 40 kg/m² or more regardless of the presence of comorbidities, or BMI between 35 and 40 kg/m² in the presence of comorbidities²².

Statistical analysis

The continuous variables were expressed as means \pm standard deviation (SD) or median. The software STATISTICA version 10 treated the data. The differences between the groups were determined by analysis of variance (ANOVA) followed by the Tukey test to compare the means or the Kruskal-Wallis test to compare data without normal distribution, followed by the Dunn test to compare the medians. The paired Student's t-test compared two means and the chi-square test (χ^2) measured the association between continuous variables. In the multivariate logistic regression model, ferritin and ferritin variation (Δ) were the dependent variables and hypertension, T2D, BMI, %EWL, and age were the independent variables. The significance level was set at 5% ($p < 0.05$).

Results

The comorbidity-free women were younger than the others, and the hypertensive women had the highest mean BMI. The three groups had similar %EWL (Ta-

ble I). Hypertension resolved in 68% and T2D in 86% of the affected women.

Diabetic women had higher baseline serum ferritin than comorbidity-free women, but not hemoglobin, which was similar between the groups (Table I). T2D increases serum ferritin: serum ferritin in baseline diabetics was 2.9 times more likely to be above the median of the study sample (Table II).

According to Weiss and Goodnough (2005)²¹ criteria, the serum ferritin of 181 (90.5%) exceeded 30 ng/mL as follows: 54.7% was between 30 and 100 ng/mL (anemia of inflammation associated with iron-deficiency anemia) and 45.3% was above 100 ng/mL (anemia of inflammation). Serum ferritin above 100 ng/dL was found in 23 (57.5%) diabetics, 28 (40%) hypertensives, and 32 (35.5%) comorbidity-free women ($p = 0.063$).

The serum ferritin of diabetics and hypertensives, and the hemoglobin of hypertensives and comorbidity-free women (Table I) decreased after RYGB. Multivariate logistic regression found that diabetics and hypertensives were, respectively, 5.5 and 3.5 times more likely to have lower endline serum ferritin (Table III).

Table I
Comparison of hypertensive, diabetic, and comorbidity-free women before (baseline) and six months after (endline) Roux-en-Y gastric bypass

Variables	Hypertensives	Diabetics	CF	p-value*
	Mean \pm SD Median (Min-Max)	Mean \pm SD Median (Min-Max)	Mean \pm SD Median (Min-Max)	
Number of women	70	40	90	
Age (years)	36.6 \pm 6.3 37.0 (22.0-45.0) ^a	37.6 \pm 6.3 40.0 (24.0-45.0) ^a	33.2 \pm 5.0 33.0 (22.0-42.0) ^b	<0.01
BMI (kg/m ²)	49.8 \pm 7.1 ^a 49.1 (35.8-73.0)	46.7 \pm 6.7 ^b 45.3 (36.5-58.9)	45.8 \pm 5.4 ^b 45.0 (36.0-69.4)	<0.05
%EWL	53.3 \pm 14.1 55.1 (22.3-85.9)	54.9 \pm 12.4 54.4 (34.6-81.1)	55.8 \pm 13.3 55.1 (30.1-85.9)	>0.05
Baseline ferritin (ng/mL)	110.1 \pm 86.3 89.0 (7.0-372.0) ^{ab}	164.8 \pm 133.4 117.4 (9.0-531.0) ^a	96.2 \pm 64.1 83.3 (8.0-391.0) ^b	<0.05
Endline ferritin (ng/mL)	88.7 \pm 80.5 61.7 (6.6-447.0)	101.2 \pm 97.7 69.4 (10.6-393.0)	87.9 \pm 63.9 75.4 (5.5-308.0)	>0.05
p-value**	<0.05	<0.05	>0.05	
Baseline Hb (g/dL)	13.5 \pm 1.1 13.5 (11.3-16.8)	13.3 \pm 1.3 13.3 (9.3-15.9)	13.2 \pm 1.0 13.2 (10.8-15.3)	>0.05
Endline Hb (g/dL)	13.0 \pm 0.9 13.1 (10.0-15.2)	13.0 \pm 1.1 13.0 (9.9-15.5)	12.9 \pm 1.0 12.9 (9.6-14.8)	>0.05
p-value**	<0.05	>0.05	<0.05	

SD: standard deviation; CF: comorbidity-free; BMI: body mass index; Hb: hemoglobin; %EWL: percentage of excess weight loss. *Variables in the same line with different letters differ according to the Tukey and Dunn tests for analysis of variance and Kruskal-Wallis test, respectively. ** Paired Student's t-test ($p < 0.05$).

Table II
Multivariate logistic regression setting serum ferritin as the dependent variable before Roux-en-Y gastric bypass (baseline)

Variables	Coefficient	Standard error	Z	p-value	Odds ratio	95%CI
Hypertension	0.481	0.350	1.373	0.170	1.617	0.814 to 3.212
T2D	1.071	0.415	2.583	0.010	2.920	1.295 to 6.576
Age	-0.487	0.311	-1.568	0.117	0.614	0.334 to 1.130
BMI	-0.210	0.298	-0.705	0.480	0.810	0.451 to 1.454

T2D: type 2 diabetes; BMI: body mass index; CI: confidence interval.

The iron deficiency rate of the study sample increased from 3.5% at baseline to 10% at endline ($p=0.010$), given by serum ferritin level below 15 ng/dL²⁰. Seventeen (8.5%) patients presented baseline anemia and 23 (11.5%), endline anemia ($p=0.317$). Of the seventeen women with hemoglobin below 12 g/dL, four had serum ferritin below 15 ng/dL (iron-deficiency anemia), ten had serum ferritin between 30 ng/dL and 100 ng/dL (anemia of inflammation associated with iron-deficiency anemia), and three had serum ferritin greater than 100 ng/dL (anemia of inflammation).

The three groups presented similar baseline iron-deficiency rates: 2.8% in the hypertensives, 5% in the diabetics, and 3.3% in the comorbidity-free women. The baseline anemia rates were also similar: 8.6% in the hypertensives, 7.5% in the diabetics, and 7.7% in the comorbidity-free women ($p>0.05$). These rates were higher but still similar between the groups at endline.

Discussion

Obesity-related chronic inflammation seems to promote the development of comorbidities, such as the metabolic syndrome and T2D, both having insulin resistance as their pathophysiological bases. These conditions can exacerbate inflammation since hyperglycemia alone can predispose individuals to chronic inflammation^{7,23}. The present results evidence this process by showing that ferritin, also an inflammatory

marker, is high in obese individuals, especially in those with T2D.

High iron stores have been associated with high risk of metabolic disorders, including, metabolic syndrome and T2D (5,9,24). Excess iron may contribute to cellular or tissue damage leading to insulin dysfunction, such as low insulin sensitivity and abnormal pancreatic β -cell secretion, through iron toxicity⁵. Regression analysis showed that T2D is a determinant of high baseline serum ferritin.

High BMI was associated with hypertension but not T2D, probably because of other etiopathogenic mechanisms required for the latter.

Endline improvement of hypertension and T2D was accompanied by a significant decrease in serum ferritin. It is possible that the resolution of baseline comorbidities promoted the reduction of endline serum ferritin. Hypertension and T2D improvement is one of the main indications for bariatric surgery because of the high proportion of individuals who no longer require medications for these conditions after surgery. Buchwald et al. (2004)²⁵ analyzed different surgical procedures and found that RYGB resolved T2D and hypertension in 84% and 67.5%, respectively, of their samples, a finding that corroborates the present finding. If, on the one hand, bariatric surgery facilitates the resolution of anemia of inflammation, on the other, it increases susceptibility to iron-deficiency anemia.

Baseline anemia found in 8.5% of the study sample was also reported by Drygalski et al. (2011)¹⁴, who found an even higher frequency of 12%, increasing

Table III
Multivariate logistic regression setting serum ferritin variation (Δ) before (baseline) and six months after (endline) Roux-en-Y gastric bypass as the dependent variable

Variables	Coefficient	Standard error	Z	p-value	Odds ratio	95%CI
Hypertension	1.252	0.369	3.389	0.001	3.497	1.695 to 7.213
T2D	1.699	0.438	3.878	<0.001	5.471	2.318 to 12.916
Age	-0.629	0.328	-1.909	0.056	0.534	0.281 to 1.017
%EWL	-0.082	0.314	-0.260	0.795	0.921	0.498 to 1.705

T2D: type 2 diabetes; %EWL: percentage of excess weight loss; CI: confidence interval.

another 4% in menopausal women 6 months after RYGB, close to the increase of 3% seen in the present study. Ruz et al. (2009)²⁶ found a prevalence of anemia of 9% in women of childbearing age six months after RYGB, which is lower than the 11.5% found by the present study. Changes in menstrual flow, resolution of amenorrhea, and higher blood flow occur after surgery, which may lead to iron-deficiency anemia in women of childbearing age¹⁴. Likewise, low nutrient ingestion and absorption and inadequate nutrient supplementation may increase the prevalence of anemia associated with bariatric surgery. Additionally, type of surgery, especially malabsorptive procedures compared with purely restrictive procedures, influences the prevalence of anemia, which also varies over time²⁷.

The study results draw attention to the specificity of the diagnosis of anemia at baseline: serum ferritin below 15 ng/dL associated with iron deficiency was found in only one-fourth of the anemic women.

Lower endline hemoglobin was not found only in diabetics. A decrease in hemoglobin six months after bariatric surgery has been reported by other studies¹⁷.

In the absence of inflammation, ferritin is considered a precise indicator of organic iron stores²⁴. Lower serum ferritin after bariatric surgery may stem not only from the loss of adipose tissue, which decreases inflammation, but also from low dietary iron intake.

Ten percent of the study women had endline iron deficiency, a finding corroborated by Ruz et al. (2009)²⁶, who reported a rate of 9%. However, other studies found iron deficiency rates ranging from 4%¹⁵ to 21%²⁸. Although these studies used serum ferritin as marker of iron deficiency, they used different cutoff points, so comparison with them is challenging. The use of serum iron or total iron binding capacity to determine iron deficiency also hinders comparison¹⁶.

This retrospective study evidenced variations in iron-related variables before and after bariatric surgery promoted by obesity-related comorbidities. Controlled studies including other iron status and inflammation indicators may contribute to the present findings.

The prevalence of iron deficiency and anemia in bariatric patients by comorbidity has not been investigated. Although the proportion of changes after bariatric surgery has not differed significantly between the study groups, surgery affected hemoglobin and serum ferritin in women with baseline T2D and hypertension. The resolution of comorbidities is an expected outcome in the surgical treatment of obesity, along with adipose tissue loss, strongly related to the inflammatory component^{1,25}. High serum ferritin suggests systemic inflammation, which may be related to a higher risk of coronary disease, especially in diabetics²⁹.

Conclusion

High serum ferritin in obese premenopausal women was associated with the main obesity-related comorbi-

ditities. T2D was a determinant of high baseline serum ferritin, and both T2D and hypertension were determinants of lower endline serum ferritin. These results reinforce the complex nature of obesity as it interacts with different metabolic pathways in the genesis of its comorbidities.

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