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PHYSIOLOGY RESEARCH

Trace Element Status and Inflammation Parameters after 6 Months of Roux-en-Y Gastric Bypass

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Abstract
Background Knowledge about the practical consequences of the nutritional status of Fe, Zn, and Cu and inflammation in obesity is limited. The objective of this study was to evaluate changes on trace element status and their potential associations with selected inflammation parameters in patients after Roux-en-Y gastric bypass (RYGBP).
Methods Sixty-three women (mean age, 36.9±9.2 years, body mass index, 43.8±4.3 kg/m^2) were evaluated at baseline and 6 months after RYGBP. Anthropometric (weight, waist circumference), body composition (fat mass and fat-free mass), dietary (nutrient intakes), and metabolic and inflammation (glucose, insulin, HOMA-IR, adiponectin, HDL-cholesterol, LDL-cholesterol, triglycerides, hs-CRP, leukocytes, polymorphonuclear neutrophils (PMN)) parameters were determined in addition to selected indices of Fe, Zn, and Cu status.
Results All but one (HDL-cholesterol) metabolic and inflammation parameters had significant differences when compared before and after RYGBP. Hemoglobin, serum ferritin, the size of the rapidly exchangeable zinc pool, and plasma copper decreased after RYGBP. Plasma and hair zinc, as well as zinc protoporphyrin increased. The change in Hb was significantly associated ($p<0.05$) to the change in leukocytes ($r=0.33$) and adiponectin ($r=-0.44$). Zinc protoporphyrin change was associated to the change in PMN ($r=0.32$) and HDL-cholesterol ($r=-0.29$). No other associations between the changes of the rest of Fe, Zn, and Cu parameters with the changes of any of the metabolic and inflammation parameters were observed.
Conclusion RYGBP produced significant weight and fat mass losses, with improvement of metabolic and inflammation parameters. Iron, zinc, and copper status were impaired after the surgery.

Keywords Iron · Zinc · Copper · Inflammation · Gastric bypass · Morbid obesity

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Introduction

During the last decades, obesity has become a major health problem worldwide [1–3]. Regarding morbid obesity, medical treatments have shown little or null effectiveness in the long-term [4]. Bariatric surgery has become increasingly used to correct this condition. Results have been positive in a number of relevant aspects, such as: maintained weight reduction, reduction of the inflammatory status, and decreased prevalence of hypertension, diabetes, and dyslipidemia [4–9]. These procedures, however, are not exempt of complications; some of them are early consequences of the surgical procedure, such as anastomotic leakage and postoperative bleeding of gastric staple line [10], while others are result of the anatomical alterations of the digestive tract [2]. Micronutrient deficiencies are common after gastric bypass [11, 12]. Among minerals, iron and calcium deficiencies have frequently been described in the literature. Anemia, for instance, can be present in 50% of the patients. The main, although not exclusive, cause of this condition, especially in non-menopausal women, is iron deficiency [12]. Information regarding other trace element deficiencies is limited. There is a report on increased prevalence of low plasma zinc from 30% previous to laparoscopic Roux-en-Y gastric bypass (RYGBP) to 36% after 1 year of the surgery [13]. Recently, our group has documented a dramatic reduction of both iron [14] and zinc [15] absorption after gastric bypass. On the other hand, obesity is associated to a pro-inflammatory condition [6], but the participation of iron, zinc, and copper in inflammation is only partially known [16–18]. The objective of this study was to evaluate changes on trace element status and their potential association with selected inflammatory parameters in seriously obese patients after RYGBP.

Materials and Methods

Subjects

Sixty-three women (mean age, 36.9±9.2 years; weight, 111.1±14.3 kg; body mass index (BMI), 43.8±4.3 kg/m^2; waist circumference, 116.7±10.4 cm; percentage fat mass, 47.1±4.3 %; and fat mass, 52.0±9.5 kg) with severe or morbid obesity who qualified for gastric bypass according to the NIH Consensus Development Panel on Gastrointestinal Surgery for Severe Obesity criteria participated in this study [19, 20]. All patients who accepted to enter into the study signed an authorized consent form. All procedures were approved by the Ethics Committee for Human Investigation of the Faculty of Medicine of the University of Chile.

Surgical Procedure

Briefly, it consisted of a 95% distal gastrectomy with resection of the excluded stomach, leaving a small gastric pouch of 15 to 20 mL. Then, an end-to-side gastrojejunostomy with circular stapler Nº 25 was performed. The length of the Roux-en-Y loop was 125 to 150 cm. Details of the procedure are available elsewhere [10].

Design

Our group has been involved in two major trials in which the main outcome has been the study of the effects of gastric bypass on the absorption of iron and other minerals and their underlying mechanisms. In the first study, carried out between 2004 and 2008 [14, 15], after undergoing gastric bypass, the subjects were randomly allocated to a vitamin and mineral supplementation protocol, the "standard vitamin–mineral supplementation", which corresponded to the routine protocol in effect at the time the trial was carried out. It consisted of one tablet per day of Larotabe® (Laboratorio Bayer de Chile, Santiago, Chile) and two tablets per day of a calcium and vitamin D supplement (640 mg Ca and 250 IU vitamin D per day) Elcal D® (Laboratorio Andromaco, Santiago, Chile). See details in Table 1. The second group, the "improved vitamin–mineral supplementation", received a specially designed tablet that provided daily at least one RDA (recommended dietary allowance) of selected micronutrients, including iron and zinc [21, 22] (Table 1). One of the main observations of the referred trial was the dramatic and maintained reduction of iron and zinc absorption. As a result, in a second trial, currently underway, all individuals undergoing gastric bypass receive an "extra iron/zinc supplement". It consists of one tablet per day of Maltofer Vit® and one tablet per day of Elcal D plus® (Laboratorios Andromaco, Santiago, Chile (Table 1)).

For the purposes of the present study, individuals with available information of trace element status and inflammation parameters before and 6 months after gastric bypass were included. Thus, those who received the "standard vitamin–mineral supplementation" were considered as group A (n=20), those who received the "improved vitamin–mineral supplementation" as group B (n=20), and those with the "extra iron/zinc supplement" as group C (n=23).

All patients followed all routine standard post-surgical procedures developed for this type of surgery at the Department of Surgery of the University of Chile's Clinical Hospital: during the first month, the subjects were fed with 500 mL/d of a liquid diet, made from chicken breast, egg white, spinach, carrots, and potatoes, which provided 800 kcal, 60 g of protein and 3.9 mg of iron, 2.9 mg of zinc, and 0.34 mg of copper, among other nutrients. A full medical control was carried out at the end of the month. One unit of a multivitamin supplement (TOL12®; Saval Laboratories, Santiago, Chile) was prescribed to be administered intramuscularly. The supplement contained 200 mg of thiamin chlorhydrate, 100 mg of pyridoxine chlorhydrate, and 10 mg of cyanocobalamine. A solid diet, fractioned in five or six meals, was prescribed after the first month and provided approximately 1,000 kcal and 60 g of proteins. During the third month, a second medical control, which included some hematological tests, was conducted and, if anemia or a risk for this condition was present, therapeutic doses of oral iron supplements were prescribed. Likewise, if alopecia signs were detected, zinc supplements were prescribed.

Table 1 Composition of the vitamin–mineral supplements used by the participants 6 months after Roux-en-Y gastric bypass

	Standard supplement group A	Improved supplement group B	Extra Fe/Zn supplement group C
Calcium (mg)	640	1,000	750
Mg mg	–	–	30
Zinc (mg)	7.5	15	25
Iron (mg)	–	18	60
Copper (µg)	1,000	900	3,000
Selenium (µg)	15	55	–
Manganese (mg)	1.5	–	5
Iodine (µg)	–	–	200
Chromium (µg)	–	–	50
Molibdenum (µg)	–	–	50
Beta carotene (mg)	3	3	–
Vitamin C (mg)	250	100	100
Vitamin E (mg)	200	200	30
Folic acid (µg)	–	400	1,000
Thiamin (mg)	–	–	3
Riboflavin (mg)	–	–	3
Vitamin B6 (mg)	–	–	10
Vitamin B12 (µg)	–	–	10
Niacin (mg)	–	–	30
Biotin (µg)	–	–	100
Panthotenic acid (mg)	–	–	7
Vitamin A (µg)	–	200	1,200
Vitamin D (IU)	250	800	800

A careful control of the amount of iron, zinc, and copper intake from supplements was kept throughout the study. This was carried out by a monthly register of pills provided by study protocol and by counting those remaining in the container. Also, a periodic check of the medical record was made for any indication of additional supplements. The amount consumed was confirmed with the subject by an interview.

Determinations

The following determinations were carried out in all subjects before and 6 months after RYGBP:

Anthropometric and Body Composition Evaluations

Weight, height, and waist circumference were measured using standardized procedures [23]. BMI was calculated. Body fat mass and fat-free mass were measured by dual energy X-ray absorptiometry using a Lunar DPX-L® densitometer (Lunar, Madison, WI, USA).

Metabolic and Inflammation Assessment

Fasting venous blood samples were obtained to assess glucose [24], total cholesterol [25], HDL-cholesterol [26], and triglycerides [27] concentrations. Plasma insulin was measured with a radioimmune-assay kit specific for human insulin (Immulite®, Clinitest, Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin resistance index (HOMA-IR) was calculated using glucose and insulin fasting values according to the HOMA method (Homeostasis Modeling Assessment) [28]. Highly sensitive c-reactive protein (hs-CRP) was measured by the method of Eda et al. [29]. Plasma adiponectin was determined by RIA (Linco Research Inc, St Charles, MO, USA). Total leukocytes, lymphocytes, and polymorphonuclear neutrophils (PMN) were assessed by coulter counter and differential count (CELL-DYN 1700®; Abbott Diagnostics, Abbott Park, IL, USA).

Dietary and Nutritional Evaluation

A 3-day record corresponding to two week days and 1 day of the weekend were filled at each evaluation period. The data registered was analyzed using a computer program (Food Processor II ®, ESHA Research, Salem, OR, USA) to calculate energy and nutrient intakes using a database which contained locally generated nutrient composition data as well as information from the literature [30].

Iron Status Hemoglobin (Hb) and mean cell volume (MCV) were determined with a coulter counter (CELL-DYN 1700®; Abbott Diagnostics, Abbott Park, IL, USA). Serum iron, total iron binding capacity, and transferrin saturation (TS) were assessed by the method of Fischer and Price [31]. Zinc protoporphyrin (ZPP) was determined using a ZP Hematofluorometer Model 206D® (AVIV Biomedical Inc, Lakewood, NJ, USA). Serum ferritin (SF) was assessed by the method suggested by the INACG [32].

Zinc Status Plasma zinc (PlZn) and hair zinc (HZn) were determined by atomic absorption spectrophotometry [33]. In a subset of 16 individuals, the size of the rapidly exchangeable zinc pool was determined using stable isotope techniques [34].

Copper Status Copper status was evaluated through the determination of plasma copper PlCu [33].

All subjects with hemoglobin concentrations <12.0 g/dL were classified as having anemia. Serum ferritin <12 ug/L was considered as low or depleted iron stores. Those who had normal hemoglobin concentrations with ≥2 abnormal biochemical measurements of iron status (MCV<80 fL or ZPP>70 ug/dL red blood cells or TS<15% or SF<12 ug/L) were classified as having iron deficiency. Iron deficiency anemia was defined as hemoglobin <12.0 g/dL plus ≥2 abnormal biochemical measurements of iron status. Low plasma zinc was considered <70 μg/dL, low hair zinc< 100 μg Zn/g, and low plasma copper<70 μg/dL.

Statistical Analysis

A two-factor repeated-measures ANOVA was used to evaluate the effects of time and type of supplement. To evaluate the association among variables, regression and correlation analyses were performed [35]. SPSS 10.0® statistical software (SPSS Inc, Chicago IL, USA) was used to perform all analyses. Because serum ferritin concentration has a skewed distribution, the values were first converted to logarithms before performing any statistical analysis. The results were then retransformed into antilogarithms to recover the original units and are expressed as geometric means and range of ±1 standard deviation. Differences were considered significant with a $p<0.05$.

Results

After 6 months of gastric bypass weight, waist circumference, and body fat loss (kilograms) were reduced on average by 27.8 %, 19.8%, and 38.8%, respectively. Dietary intakes of Fe, Zn, and Cu, regardless the supplementation group, were significantly reduced ($p<0.001$) compared with their presurgery values: Fe, 6.1±2.4 mg vs. 11.1±5.5 mg; Zn, 5.6± 1.8 mg vs. 9.6±3.9 mg; and Cu, 0.6±0.3 mg vs. 1.1±0.5 mg.

Compliance, defined as the number of vitamin and mineral pills consumed related to the total provided, ranged from 40.0% to 100% (median 94.7%).

In addition to the supplements provided by the study, 12 patients received extra iron supplements and 19 received extra zinc supplements during routine standard postsurgical procedures. The amounts, expressed as milligrams per day of the respective mineral, were added to the record of the supplements received daily as part of the study protocol in order to quantify the total mineral intake through supplements. Thus, on average, the subjects from groups A, B, and C received a total of 3.7±11.5 mg/d, 16.4±12.2 mg/d, and 61.9±28.7 mg/d of elemental iron, respectively. In terms of supplemental (elemental) zinc and copper, the corresponding numbers were: group A, 7.2± 3.1 mg Zn/day and 0.8±0.06 mg Cu/day; group B, 10.5± 3.3 mg Zn/day and 0.6±0.1 mg Cu/day; group C, 22.4± 3.4 mg Zn/day and 2.5±0.3 mg Cu/day.

A two-factor repeated-measures ANOVA was conducted to test the effects of time (month 0 vs month 6) and type of supplementation (standard vs improved vs extra Fe/Zn) on a series of variables, such as: Hb, MCV, ZPP, TS, PlZn, HZn, PlCu, hs-PCR, and leukocytes and PMN counts. The type of supplementation had no effect on any of these parameters ($p>0.05$; data not shown). Thus, although information is presented in Tables 2 and 3 by group, main analyses are discussed considering all three groups combined.

Table 2 shows the metabolic and inflammatory parameters evaluated in the study. With the only exception of HDL-cholesterol, all parameters decreased significantly after 6 months of the RYGBP. The most dramatic changes were noted for insulin, HOMA-IR, and hs-CRP.

Table 3 shows the results of Fe, Zn, and Cu status. After RYGBP, Hb, SF, and plasma Cu decreased significantly. Plasma and hair zinc concentrations increased after the surgery. The numbers of individuals with low serum ferritin increased from five to 14 after the surgery. Iron deficiency anemia was detected in two subjects before and in four individuals after the surgery. The number of cases with low plasma and hair zinc concentrations remained unchanged (two individuals) and decreased from six to four subjects, respectively. Low plasma copper was absent at the beginning of the study, and after 6 months, three patients were identified with this condition.

The magnitude of weight loss was significant ($p<0.05$) and positively associated to the change of fat mass ($r=0.77$), triglycerides ($r=0.33$), fasting insulin levels ($r=0.30$), HOMA-IR ($r=0.39$), leukocytes ($r=0.55$), PMN ($r=0.38$), and Hb ($r=0.34$). The change (final–initial) in fat mass (as

Table 2 Metabolic and inflammatory parameters preoperatory and 6 months after Roux-en-Y gastric bypass

Variable	Group A, n=20		Group B, n=20		Group C, n=23		All cases, N=63	
	Month 0	Month 6	Month 0	Month 6	Month 0	Month 6	Month 6-month 0[b]	p Value*
Insulin (µg/mL)	23.7±14.9[a]	6.9±3.3	34.3±14.3	12.5±5.8	20.6±12.9	5.2±2.3	−62.5±18.8	<0.001
Glucose (mg/dL)	99.0±18.9	83.8±9.4	102.8±20.4	87.0±8.5	115.3±54.3	81.6±8.1	−14.9±117.4	<0.001
HOMA-IR	6.0±4.0	1.5±0.8	8.9±4.7	2.7±1.3	5.5±3.7	1.0±0.5	−67.6±18.6	<0.001
Total cholesterol (mg/dL)	211.5±33.4	160.1±29.6	188.6±33.6	162.7±36.4	184.2±30.7	139.8±27.1	−19.1±16.5	<0.001
LDL-cholesterol (mg/dL)	131.2±28.2	92.7±31.2	111.5±29.7	94.1±30.0	111.3±30.7	78.6±20.3	−21.4±27.4	<0.001
HDL-cholesterol (mg/dL)	47.6±12.2	48.1±10.3	46.4±9.4	48.0±11.1	44.5±9.8	44.3±16.6	3.8±21.2	0.479
Triglycerides (mg/dL)	163.4±56.9	96.2±24.8	153.4±50.5	102.8±38.3	160.5±82.9	96.3±45.1	−34.6±21.3	<0.001
hs-CRP (mg/L)	6.1±5.2	1.9±3.4	10.1±9.3	4.3±7.4	6.3±3.9	1.3±1.8	−67.7±41.2	<0.001
Leukocytes (/uL)	7680±1338	6440±1609	7860±1637	6650±1711	7750±2095	6781±2625	−13.1±20.0	<0.001
PMN (/uL)	4294±1012	3518±1154	4464±1177	3727±1295	4164±1060	3788±1486	−15.9±20.4	<0.001

HOMA-IR Homeostasis Modeling Assessment Insulin Resistance Index, *PMN* polymorphonuclear neutrophils

[a] Mean ± SD

[b] Percent of initial value

*p value RM ANOVA effect time

kilograms) was positively associated with the change in Hb, leukocytes, PMN, and hs-PCR ($p<0.05$).

The change in Hb was significantly associated ($p<0.05$) to the change in leukocyte count ($r=0.33$) and adiponectin ($r=-0.44$). The change in zinc protoporphyrin was associated to the change in PMN ($r=0.32$) and HDL-cholesterol ($r=-0.29$). No other associations were observed between the changes of any of the other Fe, Zn, and Cu parameters with the changes of any of the metabolic and inflammation parameters.

Discussion

Gastric bypass has shown to be an effective procedure to induce not only significant weight, fat mass, and visceral fat

Table 3 Iron, zinc and copper indices before and 6 months after Roux-en-Y gastric bypass

Variable	Group A, n=20		Group B, n=20		Group C, n=20		All cases, N=63	
	Month 0	Month 6	Month 0	Month 6	Month 0	Month 6	Month 6-month 0[c]	p Value*
Hemoglobin (g/dL)	13.7±1.1[a]	12.9±1.6	13.6±0.8	12.8±0.6	13.1±1.2	13.0±1.4	−3.9±8.8	<0.001
MCV (fL)	85.3±6.5	85.3±6.9	86.0±4.1	86.4±3.8	85.4±5.5	86.3±7.6	0.5±3.6	0.253
ZPP (µg/dL)	61.1±30.8	63.5±35.6	64.0±12.1	66.9±17.4	68.2±15.6	84.3±25.4	15.0±38.6	0.013
Transferrin saturation (%)	24.5±10.0	28.8±10.7	22.9±7.2	21.6±10.2	24.0±8.7	22.4±10.2	6.2±49.7	0.782
Serum ferritin (µg /L)[b]	28.9 (11.8–70.9)	28.9 (14.4–57.6)	38.6 (19.8–75.4)	27.8 (11.8–65.3)	35.1 (22.2–55.5)	16.4 (5.5–49.0)	−9.1±28.1	<0.001
Plasma zinc (µg/dL)	86.2±12.3	92.9±17.5	86.7±13.7	98.7±21.6	86.6±9.5	87.5±10.7	8.6±23.2	0.007
Hair zinc (µg Zn/g hair)	138.5±35.5	159.0±30.2	141.5±24.6	163.0±38.9	162.7±90.8	171.2±92.5	14.3±24.5	<0.001
Plasma copper (µg/dL)	114.6±23.0	105.3±25.9	123.3±36.3	111.4±31.0	115.5±29.5	99.8±22.6	−9.1±17.2	<0.001

MCV mean cell volume, *ZPP* zinc protoporphyrin

[a] Mean ± SD

[b] Geometric mean (range±1SD)

[c] Percent of initial value

*p value RM ANOVA effect time

losses, but also improvement in metabolic parameters in the short (6 months) [36] and long-term (10 years) [4]. The magnitude of the changes observed in the present study was highly significant and, in general, in agreement with previous observations [6, 37]. We also observed a dramatic decrease of selected parameters of inflammation, such as leukocytes, PMN, and hs-CRP. The relationship between obesity and inflammation has attracted attention because it allows a better understanding of some of the consequences of this disease, as well as providing information on some of the underlying mechanisms of the positive effects of bariatric surgery in severe and morbid obesity. For instance, adipose tissue secretes adipokines such as tumor necrosis factor (TNF-α), leptin, interleukin 6, angiotensinogen, and plasminogen activator inhibitor–1, which regulate energy intake and energy expenditure, but are also involved in inflammation [6–9, 38, 39]. Adiponectin is also produced by adipocytes, and it is associated with an improvement of insulin sensitivity and the inhibition of vascular inflammation [38–40]. In our study, adiponectin was available in 40 individuals (data not shown) and increased by 45% after 6 months of RYGBP.

In contrast with the recognized positive effects of gastric bypass, the development of micronutrient deficiencies after this type of surgery is not uncommon. In terms of adverse nutritional consequences, iron deficiency and iron deficiency anemia are the most prominent findings [11, 12, 41]. Iron deficiency has been reported in 15% to 60% of patients who undergo gastric bypass [12, 41]. Major causes are decreased iron intake, decreased red meat intake, which translates into less highly available iron, and reduced iron absorption [42]. We have recently provided solid evidence on the impact of gastric bypass on iron absorption capacity [14]. Furthermore, there was a significant decrease of iron status parameters, which suggested that the iron nutritional condition was indeed impaired. We have also presented preliminary information regarding impaired zinc absorption after gastric bypass [15]. Information on zinc status after gastric bypass is very limited [13]. In the present study, we had some paradoxical results in terms of plasma and hair zinc, as they both increased after surgery. Nevertheless, interpretation of these results needs to be made with caution. It is known that inflammation reduces plasma zinc [43, 44], therefore the decrease of inflammation seen in our subjects may account, at least in part, for the increase in plasma zinc. Hair zinc presents seasonal effects [44]. Thus, given that we did not control for this factor, we cannot exclude the possibility of such effect. The size of the exchangeable zinc pool has been suggested to be a better index of zinc status [45, 46]. In 16 subjects, the results of this parameter was available (data not shown). It was significantly reduced after RYGBP, which suggests that zinc status was also impaired. We used plasma copper to assess copper status, and results showed a significant decrease in the concentrations after surgery.

In our study, a number of associations between inflammatory and metabolic parameters and Fe indices were observed. The relationship between minerals and the inflammation process is complex. On one side, the presence of inflammation modifies their metabolism producing alteration of some indices, as mentioned above, and on the other, the nutritional status of these minerals affect inflammation. Iron and copper are both pro-oxidant, as they can take part of Fenton's reaction, and antioxidant because they are part of catalase and Zn–Cu superoxide dismutase (SOD), respectively [47, 48]. Zinc has antioxidant properties by protecting protein sulfhydryl bonds from oxidation and as part of Zn–Cu SOD [49]. The knowledge about practical consequences of the interactions among Fe, Zn, and Cu and inflammation in the context of obesity and bariatric surgery is very limited. Whereas iron excess can be harmful because its oxidant capacity, iron deficiency could also stimulate inflammation according to data obtained in animal models [17]. Zinc deficiency decreases PPAR-γ and PPAR-α in endothelial cells [50]. Endothelial inflammation has been reported in obese patients [8]. Like iron, copper excess could increase oxidation damage, but copper deficiency has also been associated to exaggerated inflammatory response in rats [51]. In our study, the only associations among changes of inflammatory and metabolic parameters and changes of Fe, Zn, and Cu indices were decreased Hb and leukocytes with increased adiponectin.

In conclusion, RYGBP produced significant weight and fat mass losses, accompanied with improvement of metabolic and inflammation parameters. Iron, zinc, and copper status appear to be impaired after surgery. These results warrant further studies with longer observation periods, different levels of mineral supplementation, and additional and more sensitive parameters of inflammation.

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