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Assessment of Serum Copper in Patients with Anemia after Bariatric Surgery

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ABSTRACT
Background: Bariatric surgery interferes with food absorption, which may cause deficiencies in certain elements and complications. Copper deficiency after bariatric surgeries may be misdiagnosed, which may cause serious diseases.
Objective: The current study aimed to investigate the significance of serum copper level in the early detection of anemia related to bariatric surgery.
Patients and methods: This study included 50 participants from both sexes divided into 25 anemic patients after bariatric surgery and 25 healthy individuals. Full history taking and complete clinical examination were performed for all participants. Laboratory investigations included hemoglobin (Hb) measurement, serum copper measurement, and iron parameters including serum iron, ferritin, total iron binding capacity (TIBC), and transferrin saturation.
Results: There was a highly statistically significant decrease in Hb, serum iron, copper, and ferritin levels after bariatric surgery while transferrin level and TIBC were significantly higher in cases than their controls (P <0.001 for each), while transferrin level and TIBC were significantly higher after bariatric surgery compared to controls (P <0.001 for each). There were highly statistically significant positive correlations between copper level and each of serum hemoglobin (r= 0.726, P=0.03) and iron level (r=0.986, P <0.001), while there were significant negative correlations between copper level and each of transferrin level (r=-0.617, P=0.005) and TIBC (r=-0.520, P=0.008).
Conclusion: Copper deficiency after bariatric surgery is associated with iron deficiency anemia. So, copper supplement in addition to iron supplement after bariatric surgery is necessary to avoid the occurrence of anemia.
Keywords: Serum Copper, Anemia, Bariatric Surgery.

INTRODUCTION
Copper is an essential trace element and a component of multiple proteins and metalloenzymes which perform important metabolic functions [1]**.** It is involved in the formation of RBCs, absorption, and utilization of iron. So, hypocupremia is considered a cause of hematological problems like anemia, and bone and neurological manifestations [2]**.** Copper deficiency can be represented as microcytic, normocytic, or macrocytic anemias [3]**.**

The main sites of absorption of copper in humans are the stomach and proximal part of the small intestine, but absorption can be impaired after upper gastrointestinal surgery [4]**.** Bariatric surgery became a popular solution for morbid obesity [5]**.** Bariatric surgery includes multiple procedures such as gastric bypass surgery, biliopancreatic diversion with duodenal switch, and sleeve gastrectomy. All of them aimed to reduce stomach size, and decrease the absorption of food in obese patients [6]**.**

Unfortunately, Bariatric surgery interferes with the absorption of certain nutritional elements, causing serious nutritional deficiencies and complications. Some of these nutritional elements are already screened for after surgery, including protein, vitamin B12, vitamin D, calcium, and iron. Others that are not routinely screened for include B vitamins, fat-soluble vitamins, and minerals such as copper and zinc [7]**.**

In many cases of copper deficiency with documented hematological abnormalities (anemia), symptoms were related to iron or vitamin B12 deficiency. If patients failed to respond to ordinary treatments, severely low copper levels were detected. Treatment with copper rapidly improved the hematological abnormalities. Thus, copper deficiency after bariatric surgeries may be misdiagnosed resulting in serious diseases [8].

The current study aimed to evaluate the significance of serum copper level in the early detection of anemia related to bariatric surgery.

PATIENTS AND METHODS
This case-control study was conducted in the Clinical Hematology Unit, Internal Medicine Department, Zagazig University, and the Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University.

The study included 50 participants from both sexes divided into 25 anemic patients after bariatric surgery and 25 healthy individuals.

The age of the included participants was more than 18 years. Patients with known hematological diseases were excluded from the study.

Complete history taking including drug history and complete clinical examination was performed for all participants. Measurement of hemoglobin (Hb), serum copper, serum iron, ferritin, total iron binding capacity (TIBC), and transferrin saturation was performed.

Ethical consent:

The study got approval from the Institute Review Board, Faculty of Medicine, Zagazig University (ZU-IRB#4740\25-7-2018). All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is

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the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 22 for windows. Qualitative data were defined as numbers and percentages. The Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by the Shapiro Walk test. The normal distribution of variables was described as means and SD, and an independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Both cases and controls were matched in age and sex as there was no statistically significant difference between them (P=0.07 and 0.517, respectively). However, the weight and BMI of the studied cases after surgery were significantly more than their controls (P <0.001 for each) (**Table 1**).

Table (1): Demographic and clinical data of the studied groups.

Variables	Cases (N=25)		Controls (N=25)		t-test	P-value
	Mean ± SD		Mean ±SD			
Age (years)	37.6 ± 4.31		35.8 ± 4.91		1.85	0.07
Weight before surgery (kg)	146.8 ± 16.81		88.6 ± 2.47		17.1	<0.001**
BMI (kg/m^2)	37.8 ± 1.87		30.4 ± 1.04		17.2	<0.001**
Sex	**N**	**%**	**N**	**%**	**X^2**	**P**
Male	5	20.8	8	33.3		
Female	19	79.2	16	66.7	0.949	0.517

**: highly significant difference. BMI: body mass index.

There was a highly statistically significant decline in the levels of hemoglobin, serum iron, serum copper, and ferritin in the cases in comparison with the control group (P <0.001 for each), while transferrin level and TIBC were significantly higher in cases than their controls (P <0.001 for each) (**Table 2**).

Table (2): Biochemical results in the studied groups.

Variable	Studied group Mean ± SD		t-test	P-value
	Cases N=25	Controls N=25		
Hb (gm/dL)	10.1 ± 0.24	12.1 ± 0.78	12.5	<0.001**
Serum iron (ug/dL)	56.8 ± 3.12	103.2 ± 11.4	19.7	<0.001 **
Serum ferritin (ug/L)	36.2 ± 8.42	186.6 ± 8.52	52.51	<0.001 **
Transferrin (mg/mL)	385.2 ± 4.81	232 ± 14.72	48.9	<0.001 **
TIBC (ug/dL)	379.4 ± 22.2	249.7 ± 6.97	27.7	<0.001 **
Copper (ug/dL)	65.0 ± 3.91	113.4 ± 8.63	25.5	<0.001**

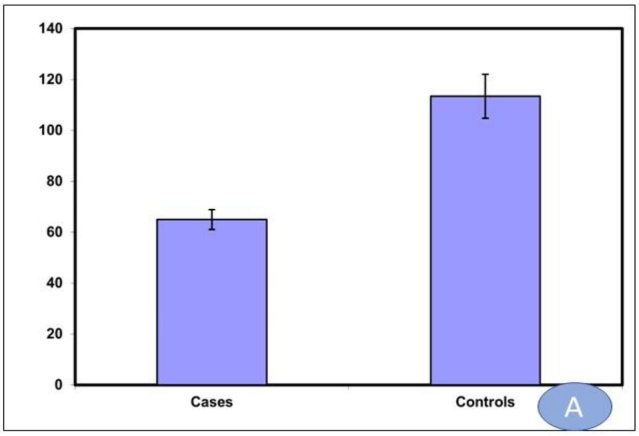
**: highly significant difference. TIBC: total iron binding capacity.

There were statistically significant positive correlations between copper levels and each of serum hemoglobin (P=0.03) and iron levels (P <0.001). However, there were significant negative correlations between copper levels and each of transferrin level (P=0.005) and TIBC (P=0.008) (**Table 3**).

Table (3): Correlations of copper levels with iron parameters.

Variable	Copper	
	r	P value
Hb	0.726	0.03*
Serum iron	0.986	<0.001**
Serum ferritin	0.227	0.111
Transferrin	-0.617	0.005*
TIBC	-0.520	0.008*

**: highly significant difference, *: significant difference. TIBC: total iron binding capacity



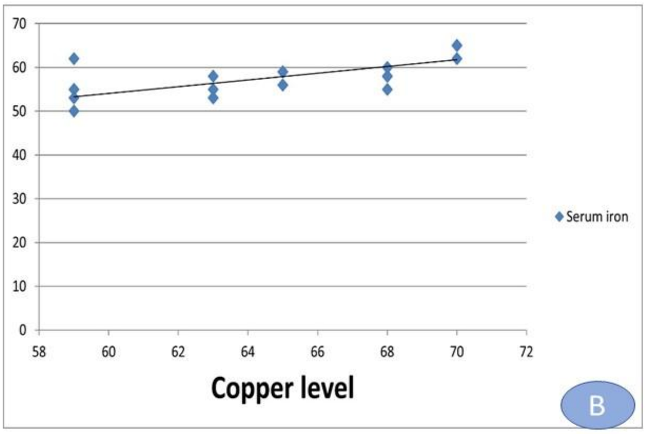


Figure (1): A: Serum copper levels (ug/dL) in the studied groups. **B:** shows a positive correlation between serum iron and copper levels in the studied cases (r=0.986, P <0.001).

DISCUSSION

Bariatric surgery is considered a safe procedure for weight reduction compared with other traditional therapies, especially when performed by experienced surgeons **[9].** However, patients after surgery are liable to nutritional deficiencies including copper, iron, and many vitamins. The selection of appropriate nutrient salts and the change in dosage forms of the supplementations can improve nutrient replacement and improve bioavailability **[10].**

In our study, there were no significant differences regarding age or sex. While weight and BMI of the studied cases who underwent surgery were significantly higher than their controls which decreased after surgery. This finding was similar to what was found by **von Drygalski *et al.* [11].** They reported that there was significant weight loss twelve months after bariatric surgery.

In our study, there was a highly statistically significant decline in the levels of hemoglobin, serum iron, and ferritin among the studied cases, while transferrin level and TIBC were significantly higher among cases than their controls. These findings were similar to those found by **Gowanlock *et al.*** [12]**.** In their study, they evaluated the hematological parameters including iron, in 388 patients with a mean follow-up of 31 months. Iron deficiency was reported in 43% of participants.

von Drygalski *et al.* [11] also reported that twelve months after surgery, iron status is most commonly affected involving serum iron, serum ferritin, or transferrin saturation. They noticed a decline in hemoglobin and ferritin levels. Ferritin level is known to be increased during inflammatory states, so it cannot be an accurate estimate of iron stores in inflammatory conditions such as obesity. So, a post-bariatric decrease in ferritin levels can be explained by both resolving of inflammation and iron store depletion.

In our study, cases and controls had a statistically significant difference as regard levels of serum copper which was higher among controls. This finding was similar to that found by **Pareek *et al.* [13].** They found that the mean copper levels decreased after bariatric surgery.

Our results demonstrated a highly statistically significant positive correlation between serum copper levels and serum iron levels; however, a significant negative correlation between serum copper levels and transferrin levels was detected. In controversy, it was discovered that intestinal mucosa and blood copper levels were enhanced in iron deprivation. They provided an explanation, citing the function of copper transporting ATPase 1 in enterocytes (Atp7a). It was upregulated in iron depletion **[14]**. Also, the main iron importer in the intestine, Dmt1, could act as a copper transporter in iron depletion **[15]**.

Copper availability competes with iron metabolism and homeostasis. Studies showed that the low serum copper levels increased iron stores in the liver due to the downregulation of ferroportin-1 and decreased activity of ceruloplasmin ferroxidase with subsequent inhibition of the export of hepatic iron **[16].**

Copper is a crucial micronutrient for both humans and animals. It plays a crucial part in cuproenzymes, which are cellular transporters and cofactors for several enzymes. Therefore, copper is crucial for the proper functioning of metabolic processes such as the production of hemoglobin, the oxidation of iron, the biosynthesis of neurotransmitters, cellular respiration, the generation of pigment, and the development of connective tissue **[17]**.

Iron is essential for practically all cells in our body since it participates in several metabolic activities such as oxygen transport, DNA synthesis, and the electron transport chain. Defects in iron metabolism cause anemia which is one of the most frequent diseases in humans. The mechanism of iron metabolism is controlled by the feedback regulation of gene products and regulatory proteins **[16].**

Normal erythropoiesis requires copper and deficiency in copper causes iron-deficiency-like anemia. Copper metabolism is linked to iron hemostasis. Both are absorbed in the proximal small intestine. Additionally, some tissues showed a close relationship between iron and copper. In the liver, iron deficiency causes hepatic copper accumulation, and hepatic iron accumulation is detected in copper deficiency [18].

CONCLUSION

Copper deficiency after bariatric surgery is associated with iron deficiency anemia. Thus, copper supplement in addition to iron supplement after bariatric surgery is necessary to avoid the occurrence of anemia.

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