Journal of Trace Elements in Medicine and Biology 62 (2020) 126650

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Nutrition

Essential trace elements in Norwegian obese patients before and 12 months after Roux-en-Y gastric bypass surgery: Copper, manganese, selenium and zinc

Solveig Meyer Mikalsen[a,*], Jan Aaseth[b], Trond Peder Flaten[c], Jon Elling Whist[a,b], Anne-Lise Bjørke-Monsen[d,e]

[a] Laboratory of Medical Biochemistry, Innlandet Hospital Trust, 2609 Lillehammer, Norway
[b] Department of Research, Innlandet Hospital Trust, 2380 Brumunddal, Norway
[c] Department of Chemistry, Norwegian University of Science and Technology, NTNU, 7491 Trondheim, Norway
[d] Laboratory of Clinical Biochemistry, Haukeland University Hospital, 5021 Bergen, Norway
[e] Department of Clinical Science, University of Bergen, 5021 Bergen, Norway

ARTICLE INFO

Keywords:
Obesity
Bariatric surgery
Micronutrients
Trace elements
Deficiency diseases

ABSTRACT

Objectives: The objective of the present study was to assess trace element status in morbidly obese subjects before and one year after Roux-en-Y gastric bypass (RYGB) in order to identify possible deficiencies.
Methods: The study population included 46 patients in the age range 27–59 years, the majority (85 %) were women. The enrolled patients attended an eight week course on lifestyle changes before bariatric surgery. After RYGB they were recommended daily micronutrient supplements with a commonly used multivitamin-mineral tablet in addition to intramuscular vitamin B_{12} injections (1 mg) every third month for 12 months. Whole blood concentrations of Cu, Mn, Se and Zn were determined using high resolution inductively coupled plasma mass spectrometry.
Results: During the 12 months follow up after bariatric surgery, the patients had lost mean 32.3 kg and median whole blood concentrations of Cu (-16 %) were reduced, Mn (+14 %) and Zn (+6%) were increased, while the Se values were essentially unchanged. Compared with reference ranges, median postoperative concentrations of all essential trace elements were either below (Zn) or in the lower reference range (Cu, Mn, Se).
Conclusion: Essential trace elements were below or in the lower reference range twelve months after RYGB. Our results indicate a need for updated guidelines in Nordic countries for trace metal monitoring and supplements in patients after bariatric surgery, especially when gastric bypass surgery is used. Further studies are required to explore and prevent trace element deficiency related to obesity and bariatric surgery.

1. Introduction

An increasing number of obese patients are being treated with bariatric surgery. In Norway at least 3000 patients have undergone bariatric surgery every year since 2008 [1,2]. In the USA alone 252,000 bariatric procedures were performed in 2018 [3]. Although weight loss improves obesity associated comorbidities such as metabolic dysfunction with insulin resistance, type 2 diabetes (T2DM) and cardiovascular disease [4] the surgical disruption of the gastrointestinal tract renders the patients at risk of malabsorption and malnutrition. Some of these deficiencies can result in severe consequences, such as neuropathy, anemia, heart failure, and encephalopathy. Clinically significant micronutrient deficiencies are reported to be common after bariatric surgery, and patients who have underwent malabsorptive procedures, such as RYGB, are at particularly high risk for micronutrient deficiencies [5,6]. Postoperatively, all these patients are instructed to take lifelong vitamin and mineral supplements. However, concerns have been raised regarding patient compliance [7]. In this context, it is essential that patients comprehend the importance of compliance and the need for lifelong supplementation [2]. Several guidelines for postoperative monitoring after gastric bypass exist [6,8,9] and recommendations for supplementation and trace element biomarker monitoring vary,

* Corresponding author.
E-mail address: solveig.meyer.mikalsen@sykehuset-innlandet.no (S. Meyer Mikalsen).

https://doi.org/10.1016/j.jtemb.2020.126650
Received 5 August 2020; Received in revised form 21 August 2020; Accepted 16 September 2020
Available online 21 September 2020

reflecting a lack of robust evidence in this field.

It is of interest that obesity in itself has an impact on trace element status. Significant positive correlations between BMI and copper (Cu) and manganese (Mn), and negative correlations between BMI and selenium (Se) and zinc (Zn) are reported in children [10]. Obese adults are reported to have higher concentrations of Se and lower Zn in hair compared to lean controls [11].

In the present study we have determined whole blood concentrations of the essential trace elements Cu, Mn, Se and Zn in 46 Norwegian obese patients before and 12 months after RYGB. We have compared the values with Norwegian reference ranges. Since more reliable information about trace element status is considered to be obtained by investigating concentrations in blood cells or whole blood rather than in plasma, not only for zinc [12], but also for the other elements assessed in the present study we have used whole blood determinations in our evaluation [13–15].

2. Materials and methods

2.1. Study population

Patients aged 18–60 years eligible for bariatric surgery due to a BMI > 40 kg/m^2 or a BMI > 35 kg/m^2 with serious weight related comorbidities, like T2DM or cardiovascular disease, were consecutively recruited at Innlandet Hospital Trust, Gjøvik, Norway, during the period 2012–2014. Exclusion criteria were major psychiatric disorders, serious somatic disorders not related to obesity, alcohol or drug addiction, former obesity surgery and other major abdominal surgery. The enrolled patients received brief dietetic counselling six months before surgery. At the end of this period they attended an eight week course on lifestyle changes, followed by bariatric surgery.

The surgical technique used was laparoscopic RYGB, which involves transection of the upper part of the stomach leaving a gastric volume of about 30 mL, which is anastomosed to the distal jejunum, resulting in bypass of the remaining part of the stomach, duodenum and proximal jejunum [16]. Reduced size of the stomach results in earlier satiety and thus restricted food intake. Furthermore, food bypasses the duodenum and enters directly into the distal jejunum, leading to reduced absorption in the small intestine [16].

After surgery the patients were recommended daily supplementation with iron (100 mg), calcium (1000 mg) and vitamin D (20 μg) for 6 months, intramuscular vitamin B_{12} injections (1 mg) every third month for 12 months, and lifelong daily multivitamin/mineral supplements (MVM) with a commonly used supplement in Norway. The most frequently used MVM supplements in Norway contains: Cu 1.0 mg, Mn 2 mg, Se 60 μg, Zn 12 mg Mg 100 mg, Fe 15 mg, iodide 150 μg, as well as multivitamins. Recommendations for supplements and follow-up routines in the present study were essentially the same as those used in a previous Norwegian study in which the compliance during the first year for MVM was 84 % [17].

Ethical approval of the protocol was obtained by the Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway, ref. number 2012/1394. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrolment.

2.2. Sample collection, preparation and analysis

Whole blood samples were collected before surgery and 12 months after surgery. The samples were obtained from the cubital vein between 8:00 and 10:30 a.m. and collected in Vacuette Trace Element Sodium Heparin tubes (Greiner Bio-One) for trace element analyses. The samples were stored at −80 °C before analysis. Approximately 0.7 mL blood was transferred to metal-free 18 mL teflon tubes. The exact weight of each sample was measured and converted back to volume by multiplying with 1.06 g/mL (the average density of whole blood). The samples were acidified with 1.0 mL 65 % (V/V) ultrapure nitric acid, produced in-house from p.a. quality nitric acid (Merck, Darmstadt) using a sub-boiling distillation system (SubPur, Milestone, Shelton, CT). The samples were then digested using a high performance microwave reactor (UltraClave, Milestone). Digested samples were decanted into pre-cleaned 15 mL polypropylene vials (VWR, USA) and diluted with ultrapure water (Purelab Option-Q, Elga) to achieve a final acid concentration of 0.6 M. Trace element concentrations were measured using high resolution inductively coupled plasma mass spectrometry (HR-ICP-MS, Thermo Finnigan Element 2, Bremen). The sample introduction system consisted of an SC2-DX auto-sampler with ULPA filter, a prepFAST system, a concentric PFA-ST nebulizer coupled to a quartz cyclonic micro mist Scott spray chamber with auxiliary gas port, aluminium skimmer and sample cones, and an O-ring-free quartz torch and 2.5 mm injector (Elemental Scientific, Omaha, NE). The radio frequency power was set to 1350 W; nebulizer and T-connection sample gas flow were 0.75 L/ min, and 0.55 L/min, respectively. Cooling gas flow was 15.5 L/ min, auxiliary gas flow was 1.1 mL/min and additional gas consisted of 10 % methane in argon with flow rate of 0.01 L/min.

Two multi-element stock solutions (Elemental Scientific, Omaha, NE) were used in the analytical procedure, one serving as a calibrating solution and the other as a quality control. These solutions were matrix matched with the blood samples for acid strength (0.6 M ultrapure nitric acid), and by adding 160 mg/L sodium and 115 mg/L potassium (Spectrapure Standards, Oslo). Corrections for instrumental drift were done by repeated measurements of one of the multi element standards. The stability of the instrument was checked by inspection of the argon signal and measurements of 1 μg/L rhenium added as an internal standard through the prepFAST system. Repeated analysis of the same reference material (Seronorm Level 1, Sero, Norway) was used to assess the precision of the analytical procedure, showing a coefficient of variation less than 10 %. The accuracy of the method was checked by analyzing Seronorm Serum Level 1 and Level 2 reference material (Sero, Norway), showing values within 90–110 % of the certified concentrations. The detection limits for the elements studied were as follows: Cu 0.59, Mn 0,18, Se 1.5 and Zn 0.73 μg/L. Reference values for trace elements in whole blood were provided by the analyzing laboratory at the Norwegian University of Science and Technology (NTNU) based on results published in the HUNT3 study [18].

2.3. Statistical analysis

Results are presented as mean and standard deviation (SD) and compared by Student's *t*-test or Anova, and as median and interquartile range (IQR) and compared by Mann-Whitney *U* test or Kruskal-Wallis test. Chi-square test was used for categorical data. Spearman correlations were used to explore relationships between data. Tests of normality were Kolmogorov-Smirnov and Shapiro-Wilk. The SPSS statistical program (version 23) was used for the statistical analyses. Two-sided p-values$<$0.05 were considered statistically significant.

3. Results

3.1. Baseline demographics

The study population included 46 patients (age range 27–59 years) with baseline characteristics given in Table 1. The majority were women, of whom 21/39 (54 %) were of reproductive age (< 45 years). At inclusion, both women and men tended to eat more meat than fish and seafood (Table 1). During the 12 months follow-up, the percentage of daily smokers declined from 22 % at inclusion to 3 % 12 months after surgery, whereas the percentage of patients who reported use of alcohol more than once a month, remained essentially unchanged (43 % versus 41 %).

Total mean weight loss from inclusion to 12 months after bariatric surgery was 42.5 (SD 11.9) kg (range 13.4–68.7 kg). Approximately 25

Table 1
Baseline characteristics in patients admitted for gastric bypass (n = 46).

Female gender[a]	39/46 (85 %)
Age, years[b]	43.9 (9.1)
Body mass index[b]	42.4 (3.6)
Education, years[b]	13 (3)
Full time occupation[a]	23/45 (51 %)
Married/cohabitant[a]	38/44 (86 %)
Daily intake of meat, grams[b]	164 (60)
Daily intake of fish/seafood, grams[b]	80 (49)
Daily smoker[a]	10/45 (22 %)
Alcohol intake ≥ 1 per month[a]	20/46 (43 %)
Current diagnosis of hypertension[a]	15/44 (34 %)
Current diagnosis of diabetes[a]	7/44 (16 %)

[a] Data are expressed as numbers (%).
[b] Data are expressed as mean (SD).

% of weight loss was achieved by dieting and exercise before surgery (mean 10.3 (SD 4.6) kg), while 75 % was achieved after surgery (mean 32.3 (SD 10.6) kg). There was a mean reduction of 33 % in BMI from inclusion to 12 months postoperatively, with no gender difference (p = 0.81).

3.2. Trace element concentrations before and 12 months after bariatric surgery

Whole blood concentrations of the trace elements before and 12 months after bariatric surgery and percent change during follow up are given in Table 2. The concentrations of Cu, Mn and Zn changed significantly during the observation period, median concentration of Cu decreased by 16 %, while median Mn and Zn concentrations increased by 14 % and 16 %, respectively. The concentrations of Se remained essentially unchanged.

Before surgery, Cu was inversely correlated to Zn (rho: -0.37, p = 0.01). Mn was positively correlated to Zn (rho: 0.38, p = 0.007). Se was positively correlated to Zn (rho: 0.39, p = 0.03). After surgery the only positive correlation observed was between Cu and Mn (rho: 0.36, p = 0.01). Negative, weak correlations were observed between total weight loss and Cu (rho: -0.23, p = 0.13) and Mn (rho: -0.21, p = 0.16), and a weak positive correlation was seen for Zn (rho: 0.25, p = 0.10) 12 months after surgery. No correlation was seen between total weight loss and Se (rho: 0.04, p = 0.80). No significant correlations were seen between trace element concentrations and BMI, neither before (p > 0.37) nor 12 months after surgery (p > 0.19).

Before surgery CRP was positively correlated to Mn (rho = 0.29, p = 0,05) and Cu (rho = 0.36, p = 0.01). After surgery CRP was only correlated to Cu (rho = 0.48, p = 0.001). Smoking was significantly correlated to whole blood Cu before surgery (rho=-0.33, p = 0.03) whereas the correlation after surgery was marginal (rho=-0.36, p = 0.05).

Table 2
Whole blood concentrations of essential trace elements in Norwegian obese patients before and 12 months after bariatric surgery (n = 46).

Parameters	Before surgery	12 months after surgery	Percent change	p-value[a]	Reference values[b]
Copper, mg/L	1.01 (0.87, 1.11)	0.85 (0.77, 0.92)	−16%	<0.001	1.01 (0.82, 1.27)
Manganese, μg/L	6.98 (5.25, 9.34)	7.93 (5.73, 10.11)	+14 %	0.02	8.92 (5.81, 14.92)
Selenium, μg/L	76.6 (67.7, 86.8)	77.8 (68.4, 88.5)	+2%	0.85	99.3 (75.4, 136.9)
Zinc, mg/L	5.05 (4.46, 5.50)	5.34 (4.99, 5.78)	+6%	0.003	7.5 (5.90, 9.10)

[a] Data before and after surgery are given as median (25th,75th percentiles) and compared by Kruskal-Wallis test.
[b] Median (5th, 95th percentiles) from Norwegian adults (20–91 years, n=1011) [18].

4. Discussion

In this study of morbidly obese patients, who underwent gastric bypass surgery and were recommended a standardized set of dietary supplements, we found that median whole blood concentration of Cu was reduced, whereas Mn- and Zn-concentrations were modestly increased, and the median Se-concentration remained unchanged, as assessed twelve months after the surgery. Compared with reference ranges based on healthy Norwegian adults, postoperative median concentrations of the determined essential trace elements were either below (Zn) or in the lower reference range (Cu, Mn, Se). Except for Cu, the preoperative concentrations were also low.

The observed low concentrations of these trace elements may be due to obesity related factors, inappropriate intake, reduced absorption or a combination of these factors.

Low concentrations of Zn and Se [5,19] and high concentrations of Cu [20,21] have been reported previously in obese patients. Sanches et al. (2015) reported low plasma concentrations of zinc and iron, but physiological values for copper, preoperatively in a morbidly obese population in Chile [22]. Data on other essential trace elements in relation to obesity and bariatric surgery are scarce.

Postoperative changes in concentrations of the different trace elements may be related to their absorption sites in the gastrointestinal tract. Most of the Cu and Zn absorption occurs in the jejunum and duodenum [5,23], although Cu is also absorbed in the stomach [24]. RYGB surgery involves bypass of the duodenum and a significant part of the jejunum, which may explain the relatively low postoperative blood levels observed for these elements. The subnormal Zn status postoperatively in spite of supplement is in part ascribed to a disrupted Zn uptake after RYGB as is described previously [25]. Mn is also absorbed mainly in the jejunum, but the prescribed supplementations may be sufficient to make up for a diminished absorption of this element. In addition, a marginal Fe status after gastric bypass [26], is assumed to favor Mn absorption due to the interactions between these two elements [27,28]. Postoperative changes in the function of the divalent metal transporter in jejunum may have contributed to the observed absorptive disruptions [29]. The supplementation of Se appears to cover the *minimal* nutritional needs, although an optimal Se status may require higher intakes [30].

It is in accordance with generally accepted guidelines that all patients subjected to bariatric surgery are instructed to take lifelong MVM supplements [2]. Although concerns have been raised regarding the persistency of patient compliance over years [7], some Norwegian studies using the same follow-up routines as used in the present study have found a compliance of about 80 % for MVM supplement during the first year after surgery [17,31]. However, the postoperative supplements routinely used in Norway for Cu (1 mg), Zn (12 mg) and Se (60 μg) after RYGB may very well result in marginal or insufficient intakes. Thus, the American Society for Metabolic and Bariatric Surgery in recent guidelines [6] recommends up to 2 (two) MVM tablets daily after RYGB corresponding to specified doses of 2 mg for Cu and 22 mg for Zn.

In Norway the regulation of content of commercial multivitamin/mineral (MVM) supplements is described in “Forskrift om kosttilskudd” [32]. Specified in the regulation is the minimum content of minerals in any MVM per recommended Daily Value (DV); 0.15 mg for Cu, 1.5 mg for Zn, 0.3 mg for Mn, and 8.3 μg for Se.

According to the Nordic Nutrition Recommendations (NNR) the recommended dietary intake (RI) for healthy adults of Cu is 0.9 mg/day, for Se the RI is 50 μg/d for women and 60 μg/day for men, and for Zn the RI is 7 mg/day for women and 9 mg/day for men [33]. The NNR concluded that no recommendations could be given for Mn due to lack of sufficient evidence whereas The European Food Safety Authority (EFSA) has proposed an Adequate Intake (AI) of 3 mg Mn/day for adults [34].

In *healthy* individuals the actual mean daily intakes and the recommended dietary intakes are assumed to be approximately the same for most trace elements [35]. However, it appears evident from the detailed discussions by Mechanick et al. (2020) [36] that it is highly questionable whether the prescribed doses for trace element supplementation in Norway after RYGB gastric bypass, which are essentially based on these recommendations, contain sufficient and adequate amounts of trace elements for this group of patients.

In the following paragraphs our findings on the concentrations observed for the different trace elements are discussed more in detail, and the determined levels are related to the physiological roles of each element.

4.1. Copper (Cu)

The median Cu concentration in whole blood, about 1 mg/L, was reduced by 16 % during the first year after RYGB and declined then into the lower reference range (Table 2). The optimum dose of Cu supplementation for deficiency prevention is not known, but it has been suggested that MVM supplements for bariatric surgery patients should contain Cu at doses close to the RI of 0.9 mg/day [20], as was used in the present study. However, the American Society for Metabolic and Bariatric Surgery in recent guidelines [6] recommends up to 2 MVM tablets daily after RYGB surgery corresponding to 2 mg for Cu. The observed decrease in Cu indicates a marginal intake, although a minor decline in blood plasma and whole blood levels could be mediated by reduced obesity related inflammation, as both Cu concentrations and obesity are positively associated with inflammation [37].

Cu-containing enzymes are essential in intracellular oxidation-reduction reactions and in scavenging of free radicals [38,39]. Cu deficiency is rare in the general population, but can result from malnutrition or malabsorption [24]. Previous reports have indicated that such deficiency occurs in about 10 % of patients treated with gastric bypass when adequate supplementation has not been given [20]. In some cases Cu deficiency has been associated with severe anemia and myeloneuropathy [40].

4.2. Manganese (Mn)

In this study median whole blood Mn concentrations increased by 14 % during the study period, from a preoperative value of about 7 μg/L Both pre- and postoperative median values were in the lower reference range (Table 2). The human body contains 10–20 mg of Mn, of which about 40 % is in bone [41]. There is no recommended dietary intake (RI) for Mn, but a proposed Adequate Intake (AI) of 3 mg/day [34]. A daily supplementation of about 2 mg, as is used in the present study, appears to be an adequate dose.

Mn is a constituent of several enzymes, of which the mitochondrial Mn-superoxide dismutase is of particular importance for the defense against reactive oxygen species [43–45]. Mn deficiency is rare, but may result in abnormal skeletal development [46]. Toxic levels are associated with neurological damage [41,47,48]. Researchers have proposed a protective role of Mn on the occurrence of metabolic syndrome and T2DM. Thus, Kazi et al. reported on lower blood levels of Mn in diabetic patients [44]. According to Aschner et al. elevated serum glucose can be caused by low Mn concentrations, which subsequently may cause an increase in body fat [43]. The raised concentrations as observed in the present study may contribute to the observed beneficial effect of RYGB on glucose regulation [49].

4.3. Selenium (Se)

In the present study no significant change was observed for median whole blood Se which remained unchanged at about 77 μg /L. This is in the lower range of the reference interval (Table 2). The Se status of the present obese population may be considered suboptimal [50]. Decreased or suboptimal Se levels in obese individuals have been reported in previous studies [51]. Zadeh et al. recommend lifelong supplementation and regular patient monitoring [52].

Se is an essential part of antioxidative enzymes such as glutathione peroxidases and thioredoxin reductases. Se deficiency has been associated with increased risk of some types of cancer [53], cardiovascular disease and defective immune response, and severe deficiency may lead to cardiomyopathy and hypothyroidism [54–56]. Low maternal Se status is also associated with low psychomotor score in infants [57]. Se supplementation does not seem to prevent T2DM [58]. However, whole blood as well as blood plasma concentrations below 90–100 μg /L is considered suboptimal [59,60], implying that a daily supplement with 2 MVM tablets, corresponding to 120 μg/day, should be recommended after RYGB also in Norway.

4.4. Zinc (Zn)

In this study the median whole blood Zn concentration of about 5 mg/L increased modestly by 6% post-operatively, but was below the reference range (5.9–9.1 mg/L) both before and after surgery (Table 2). Zn deficiency in patients before and after bariatric surgery due to low intake and reduced absorption, have been reported previously [5,19,61]. It is evident from these observations on Zn status in obese populations that updated guidelines concerning Zn monitoring and supplementation, before and after bariatric surgery, are required. Zn supplementation should be recommended to severely obese patients both before and after bariatric surgery. The current recommendation of postoperative Zn supplementation (12 mg/day) appears to be insufficient. The American Society for Metabolic and Bariatric Surgery recommends up to 2 tablets of MVM tablets or 22 mg zinc daily after gastric bypass [6].

Zn is a cofactor for enzymes involved in protein synthesis, digestion, immunity, and regulation of gene transcription [41]. In pancreatic β-cells, Zn is involved in insulin synthesis and storage in secretory granules [62]. Furthermore, Zn may play a role in appetite control [63]. It has also been reported that inadequate maternal intake of Zn is associated with neural tube defects in the fetus [64]. This is relevant when evaluating results in populations treated with bariatric surgery, where about 75 % are women of reproductive age.

5. Strengths and limitations

In this study we have determined whole blood trace element levels in patients after moderate weight loss prior to surgery and one year after RYGB. We have taken into consideration that blood plasma values both for zinc and other elements may fluctuate more than intracellular values, and may not reflect the true whole body status of a trace element, and therefore we have used whole blood analyses in this study. Possible Zn contamination of blood specimens is known from several previous studies [65], but is not considered a probable source of error in the present study with its rigorous precautions as to sampling and analyses. However, a small sample size with only 46 participants in the present study represents a clear limitation, and this calls for further studies on larger populations of morbidly obese patient referred for bariatric surgery.

6. Conclusion

RYGB results in substantial weight loss and important health benefits. However, it is important to realize that altered anatomy of the gastrointestinal tract puts the patients into a state of constant malabsorption and possible malnutrition. The fact that the studied essential trace element blood levels were below or in the lower reference range indicates a need for updated dietary guidelines for severely obese patients after bariatric surgery, especially after gastric bypass. Our knowledge concerning the bioavailability of essential trace elements in food and supplements, and the nutritional requirements for humans, is incomplete. Our findings should encourage clinicians to be aware of deficiency symptoms after bariatric surgery. Women of reproductive age are particularly vulnerable, as deficiency of essential trace elements may have serious consequences for the offspring. Long term follow up studies on morbidly obese patients before and after bariatric surgery should be encouraged.

CRediT authorship contribution statement

Solveig Meyer Mikalsen: Conceptualization, Investigation, Writing - original draft. **Jan Aaseth:** Conceptualization, Supervision, Project administration, Writing - review & editing. **Trond Peder Flaten:** Methodology, Formal analysis, Writing - review & editing. **Jon Elling Whist:** Conceptualization, Supervision, Funding acquisition, Project administration, Writing - review & editing. **Anne-Lise Bjørke-Monsen:** Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

This research was funded by Innlandet Hospital Trust, Norway. We thank senior engineer Syverin Lierhagen at Department of Chemistry, Norwegian University of Science and Technology, for performing the HR-ICP-MS analyses.

References

[1] R. Sandbu, M. Svanevik, Bariatric surgery in Norway - full speed ahead? Tidsskr. Nor. Laegeforen. 139 (10) (2019).
[2] T.Y. Kim, S. Kim, A.L. Schafer, Medical management of the postoperative bariatric surgery patient, in: K.R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman, J.M. Hershman, G. Kaltsas, C. Koch, P. Kopp, M. Korbonits, R. McLachlan, J.E. Morley, M. New, L. Perreault, J. Purnell, R. Rebar, F. Singer, D. L. Trence, A. Vinik, D.P. Wilson (Eds.), Endotext, 2000. South Dartmouth (MA).
[3] J.I. Mechanick, C. Apovian, S. Brethauer, W.T. Garvey, A.M. Joffe, J. Kim, R. F. Kushner, R. Lindquist, R. Pessah-Pollack, J. Seger, R.D. Urman, S. Adams, J. B. Cleek, R. Correa, M.K. Figaro, K. Flanders, J. Grams, D.L. Hurley, S. Kothari, M. V. Seger, C.D. Still, Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/ American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists - Executive Summary, Endocr. Pract. 25 (12) (2019) 1346–1359.
[4] L. Sjostrom, Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery, J. Intern. Med. 273 (3) (2013) 219–234.
[5] J.J. Patel, M.S. Mundi, R.T. Hurt, B. Wolfe, R.G. Martindale, Micronutrient deficiencies after bariatric surgery: an emphasis on vitamins and trace minerals [Formula: see text], Nutr. Clin. Pract. 32 (4) (2017) 471–480.
[6] J. Parrott, L. Frank, R. Rabena, L. Craggs-Dino, K.A. Isom, L. Greiman, American Society for Metabolic and Bariatric Surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients, Surg. Obes. Relat. Dis. 13 (5) (2017) 727–741.
[7] P. Henfridsson, A. Laurenius, O. Wallengren, A.J. Beamish, J. Dahlgren, C. E. Flodmark, C. Marcus, T. Olbers, E. Gronowitz, L. Ellegard, Micronutrient intake and biochemistry in adolescents adherent or nonadherent to supplements 5 years after Roux-en-Y gastric bypass surgery, Surg. Obes. Relat. Dis. 15 (9) (2019) 1494–1502.
[8] M. Fried, V. Hainer, A. Basdevant, H. Buchwald, M. Deitel, N. Finer, J.W. Greve, F. Horber, E. Mathus-Vliegen, N. Scopinaro, R. Steffen, C. Tsigos, R. Weiner, K. Widhalm, Inter-disciplinary European guidelines on surgery of severe obesity, Int. J. Obes. (Lond.) 31 (4) (2007) 569–577.
[9] D. Heber, F.L. Greenway, L.M. Kaplan, E. Livingston, J. Salvador, C. Still, S. Endocrine, Endocrine and nutritional management of the post-bariatric surgery patient: an Endocrine Society Clinical Practice Guideline, J. Clin. Endocrinol. Metab. 95 (11) (2010) 4823–4843.
[10] Y. Fan, C. Zhang, J. Bu, Relationship between selected serum metallic elements and obesity in children and adolescent in the U.S, Nutrients 9 (2) (2017).
[11] A.A. Tinkov, M.G. Skalnaya, O.P. Ajsuvakova, E.P. Serebryansky, J.C. Chao, M. Aschner, A.V. Skalny, Selenium, zinc, chromium, and vanadium levels in serum, hair, and urine samples of obese adults assessed by inductively coupled plasma mass spectrometry, Biol. Trace Elem. Res. (2020).
[12] N.M. Lowe, K. Fekete, T. Decsi, Methods of assessment of zinc status in humans: a systematic review, Am. J. Clin. Nutr. 89 (6) (2009) 2040S–2051S.
[13] J.D. Kruse-Jarres, M. Rukgauer, Trace elements in diabetes mellitus. Peculiarities and clinical validity of determinations in blood cells, J. Trace Elem. Med. Biol. 14 (1) (2000) 21–27.
[14] P. Galloway, D.C. McMillan, N. Sattar, Effect of the inflammatory response on trace element and vitamin status, Ann. Clin. Biochem. 37 (Pt 3) (2000) 289–297.
[15] J. Aaseth, M. Haugen, O. Forre, Rheumatoid arthritis and metal compounds–perspectives on the role of oxygen radical detoxification, Analyst 123 (1) (1998) 3–6.
[16] K.D. Higa, T. Ho, K.B. Boone, Laparoscopic Roux-en-Y gastric bypass: technique and 3-year follow-up, J. Laparoendosc. Adv. Surg. Tech. A 11 (6) (2001) 377–382.
[17] E. Aaseth, M.W. Fagerland, A.M. Aas, S. Hewitt, H. Risstad, J. Kristinsson, T. Bohmer, T. Mala, E.T. Aasheim, Vitamin concentrations 5 years after gastric bypass, Eur. J. Clin. Nutr. 69 (11) (2015) 1249–1255.
[18] A. Simic, Trace Elements in the General Population and Their Possible Role in Type 2 Diabetes – the Third Nord-Trøndelag Health Survey (HUNT3) (dissertation), Norwegian University of Science and Technology (NTNU), Trondheim, 2017, 2017.
[19] K.K. Mahawar, A.G. Bhasker, V. Bindal, Y. Graham, U. Dudeja, M. Lakdawala, P. K. Small, Zinc deficiency after gastric bypass for morbid obesity: a systematic review, Obes. Surg. 27 (2) (2017) 522–529.
[20] N. Gletsu-Miller, M. Broderius, J.K. Frediani, V.M. Zhao, D.P. Griffith, S. S. Davis Jr., J.F. Sweeney, E. Lin, J.R. Prohaska, T.R. Ziegler, Incidence and prevalence of copper deficiency following roux-en-y gastric bypass surgery, Int. J. Obes. (Lond.) 36 (3) (2012) 328–335.
[21] N. Gletsu-Miller, B.N. Wright, Mineral malnutrition following bariatric surgery, Adv. Nutr. 4 (5) (2013) 506–517.
[22] A. Sanchez, P. Rojas, K. Basfi-Fer, F. Carrasco, J. Inostroza, J. Codoceo, A. Valencia, K. Papapietro, A. Csendes, M. Ruz, Micronutrient deficiencies in morbidly obese women prior to bariatric surgery, Obes. Surg. 26 (2) (2016) 361–368.
[23] R.C. Gobato, D.F. Seixas Chaves, E.A. Chaim, Micronutrient and physiologic parameters before and 6 months after RYGB, Surg. Obes. Relat. Dis. 10 (5) (2014) 944–951.
[24] D. Ellingsen, L.B. Møller, J. Aaseth, Copper, Academic press, London, 2015.
[25] M. Ruz, F. Carrasco, P. Rojas, J. Codoceo, J. Inostroza, K. Basfi-fer, A. Csendes, K. Papapietro, F. Pizarro, M. Olivares, L. Sian, J.L. Westcott, L.V. Miller, K. M. Hambidge, N.F. Krebs, Zinc absorption and zinc status are reduced after Roux-en-Y gastric bypass: a randomized study using 2 supplements, Am. J. Clin. Nutr. 94 (4) (2011) 1004–1011.
[26] I. Gesquiere, M. Lannoo, P. Augustijns, C. Matthys, B. Van der Schueren, V. Foulon, Iron deficiency after Roux-en-Y gastric bypass: insufficient iron absorption from oral iron supplements, Obes. Surg. 24 (1) (2014) 56–61.
[27] G. Bjorklund, J. Aaseth, A.V. Skalny, J. Suliburska, M.G. Skalnaya, A.A. Nikonorov, A.A. Tinkov, Interactions of iron with manganese, zinc, chromium, and selenium as related to prophylaxis and treatment of iron deficiency, J. Trace Elem. Med. Biol. 41 (2017) 41–53.
[28] J.W. Finley, Manganese absorption and retention by young women is associated with serum ferritin concentration, Am. J. Clin. Nutr. 70 (1) (1999) 37–43.
[29] A. Marambio, G. Watkins, F. Castro, A. Riffo, R. Zuniga, J. Jans, M.E. Villanueva, G. Diaz, Changes in iron transporter divalent metal transporter 1 in proximal jejunum after gastric bypass, World J. Gastroenterol. 20 (21) (2014) 6534–6540.
[30] R. Hurst, C.N. Armah, J.R. Dainty, D.J. Hart, B. Teucher, A.J. Goldson, M. R. Broadley, A.K. Motley, S.J. Fairweather-Tait, Establishing optimal selenium status: results of a randomized, double-blind, placebo-controlled trial, Am. J. Clin. Nutr. 91 (4) (2010) 923–931.
[31] S. Hewitt, T.T. Sovik, E.T. Aasheim, J. Kristinsson, J. Jahnsen, G.S. Birketvedt, T. Bohmer, E.F. Eriksen, T. Mala, Secondary hyperparathyroidism, vitamin D sufficiency, and serum calcium 5 years after gastric bypass and duodenal switch, Obes. Surg. 23 (3) (2013) 384–390.
[32] Government, Department of Justice, Forskrift om kosttilskudd, 2004. https://lovdata.no/dokument/SF/forskrift/2004-05-20-755.
[33] Nordic Council of Ministers, Nordic Nutrition Recommendations 2012 5 (11) (2014) 1, https://doi.org/10.6027/Nord2014-002.
[34] EFSA Panel on Dietetic Products, Scientific Opinion on Dietary Reference Values for Manganese, 2013, p. 3419.
[35] O. Wada, H. Yanagisawa, [Trace elements and their physiological roles], Nihon Rinsho 54 (1) (1996) 5–11.
[36] J.I. Mechanick, C. Apovian, S. Brethauer, W.T. Garvey, A.M. Joffe, J. Kim, R. F. Kushner, R. Lindquist, R. Pessah-Pollack, J. Seger, R.D. Urman, S. Adams, J. B. Cleek, R. Correa, M.K. Figaro, K. Flanders, J. Grams, D.L. Hurley, S. Kothari, M. V. Seger, C.D. Still, Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/ American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists, Surg. Obes. Relat. Dis. 16 (2) (2020) 175–247.
[37] H. Tapiero, D.M. Townsend, K.D. Tew, Trace elements in human physiology and pathology, Copper Biomed. Pharmacother. 57 (9) (2003) 386–398.
[38] N. Horn, L.B. Moller, V.M. Nurchi, J. Aaseth, Chelating principles in Menkes and Wilson diseases: choosing the right compounds in the right combinations at the right time, J. Inorg. Biochem. 190 (2019) 98–112.

[39] H. Ohrvik, J. Aaseth, N. Horn, Orchestration of dynamic copper navigation - new and missing pieces, Metallomics 9 (9) (2017) 1204–1229.

[40] D.P. Griffith, D.A. Liff, T.R. Ziegler, G.J. Esper, E.F. Winton, Acquired copper deficiency: a potentially serious and preventable complication following gastric bypass surgery, Obesity (Silver Spring) 17 (4) (2009) 827–831.

[41] J. Higdon, An Evidence-Based Approach to Vitamins and Minerals: Health Implications and Intake Recommendations, Thieme, New York, 2003.

[43] M. Aschner, T.R. Guilarte, J.S. Schneider, W. Zheng, Manganese: recent advances in understanding its transport and neurotoxicity, Toxicol. Appl. Pharmacol. 221 (2) (2007) 131–147.

[44] T.G. Kazi, H.I. Afridi, N. Kazi, M.K. Jamali, M.B. Arain, N. Jalbani, G.A. Kandhro, Copper, chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients, Biol. Trace Elem. Res. 122 (1) (2008) 1–18.

[45] L. Li, X. Yang, The essential element manganese, oxidative stress, and metabolic diseases: links and interactions, Oxid. Med. Cell. Longev. 2018 (2018), 7580707.

[46] V.L. Schramm, Manganese in Metabolism and Enzyme Function, Elsevier, Amsterdam, 2012.

[47] P. Dusek, P.M. Roos, T. Litwin, S.A. Schneider, T.P. Flaten, J. Aaseth, The neurotoxicity of iron, copper and manganese in Parkinson's and Wilson's diseases, J. Trace Elem. Med. Biol. 31 (2015) 193–203.

[48] G. Bjorklund, M.S. Chartrand, J. Aaseth, Manganese exposure and neurotoxic effects in children, Environ. Res. 155 (2017) 380–384.

[49] D. Hofso, F. Fatima, H. Borgeraas, K.I. Birkeland, H.L. Gulseth, J.K. Hertel, L. K. Johnson, M. Lindberg, N. Nordstrand, M. Cvancarova Smastuen, D. Stefanovski, M. Svanevik, T. Gretland Valderhaug, R. Sandbu, J. Hjelmesaeth, Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial, Lancet Diabetes Endocrinol. 7 (12) (2019) 912–924.

[50] U. Alehagen, P. Johansson, M. Bjornstedt, A. Rosen, C. Post, J. Aaseth, Relatively high mortality risk in elderly Swedish subjects with low selenium status, Eur. J. Clin. Nutr. 70 (1) (2016) 91–96.

[51] S.F. Azab, S.H. Saleh, W.F. Elsaeed, M.A. Elshafie, L.M. Sherief, A.M. Esh, Serum trace elements in obese Egyptian children: a case-control study, Ital. J. Pediatr. 40 (2014) 20.

[52] M. Hassan Zadeh, G. Mohammadi Farsani, N. Zamaninour, Selenium status after Roux-en-Y gastric bypass: interventions and recommendations, Obes. Surg. 29 (11) (2019) 3743–3748.

[53] A. Kuria, X. Fang, M. Li, H. Han, J. He, J.O. Aaseth, Y. Cao, Does dietary intake of selenium protect against cancer? A systematic review and meta-analysis of population-based prospective studies, Crit. Rev. Food Sci. Nutr. 60 (4) (2020) 684–694.

[54] U. Alehagen, J. Aaseth, Selenium and coenzyme Q10 interrelationship in cardiovascular diseases–a clinician's point of view, J. Trace Elem. Med. Biol. 31 (2015) 157–162.

[55] J. Bleys, A. Navas-Acien, S. Stranges, A. Menke, E.R. Miller, 3rd, E. Guallar, Serum selenium and serum lipids in US adults, Am. J. Clin. Nutr. 88 (2) (2008) 416–423.

[56] M. Laclaustra, A. Navas-Acien, S. Stranges, J.M. Ordovas, E. Guallar, Serum selenium concentrations and diabetes in U.S. adults: National Health and Nutrition Examination Survey (NHANES) 2003-2004, Environ. Health Perspect. 117 (9) (2009) 1409–1413.

[57] K. Varsi, B. Bolann, I. Torsvik, T.C. Rosvold Eik, P.J. Hol, A.L. Bjorke-Monsen, Impact of maternal selenium status on infant outcome during the first 6 months of life, Nutrients 9 (5) (2017).

[58] S. Stranges, S. Sieri, M. Vinceti, S. Grioni, E. Guallar, M. Laclaustra, P. Muti, F. Berrino, V. Krogh, A prospective study of dietary selenium intake and risk of type 2 diabetes, BMC Public Health 10 (2010) 564.

[59] A.P. Kipp, D. Strohm, R. Brigelius-Flohe, L. Schomburg, A. Bechthold, E. Leschik-Bonnet, H. Heseker, S. German Nutrition, Revised reference values for selenium intake, J. Trace Elem. Med. Biol. 32 (2015) 195–199.

[60] M.P. Rayman, Selenium and human health, Lancet 379 (9822) (2012) 1256–1268.

[61] I. Gesquiere, V. Foulon, P. Augustijns, A. Gils, M. Lannoo, B. Van der Schueren, C. Matthys, Micronutrient intake, from diet and supplements, and association with status markers in pre- and post-RYGB patients, Clin. Nutr. 36 (4) (2017) 1175–1181.

[62] G. Bjorklund, M. Dadar, L. Pivina, M.D. Dosa, Y. Semenova, J. Aaseth, The role of zinc and copper in insulin resistance and diabetes mellitus, Curr. Med. Chem. (2019).

[63] H.C. Chao, Y.J. Chang, W.L. Huang, Cut-off serum zinc concentration affecting the appetite, growth, and nutrition status of undernourished children supplemented with zinc, Nutr. Clin. Pract. 33 (5) (2018) 701–710.

[64] A. Kirksey, T.D. Wachs, F. Yunis, U. Srinath, A. Rahmanifar, G.P. McCabe, O. M. Galal, G.G. Harrison, N.W. Jerome, Relation of maternal zinc nutriture to pregnancy outcome and infant development in an Egyptian village, Am. J. Clin. Nutr. 60 (5) (1994) 782–792.

[65] J.P. Clavel, P. Lavirotte, A. Galli, [Copper, zinc and aluminum contamination of blood specimens used for determination of these metals], Pathol. Biol. (Paris) 31 (10) (1983) 851–854.