

Copper Deficiency after Gastric Bypass for Morbid Obesity: a Systematic Review

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Published online: 1 April 2016
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Abstract A large number of patients undergoing bariatric surgery are deficient in copper, and Roux-en-Y gastric bypass can further aggravate it. Delays in diagnosis and treatment of copper deficiency can leave patients with residual neurological disability. This has led to recommendation from the British Obesity and Metabolic Surgery Society that copper levels should be monitored annually after gastric bypass. This review concludes that copper deficiency in adequately supplemented patients is rare and can be adequately treated if a related haematological or neurological disorder is diagnosed. The cost of routine monitoring may therefore not be justified for adequately supplemented, asymptomatic patients who have undergone Roux-en-Y gastric bypass. The screening may however be necessary for high-risk patient groups to prevent severe complications and permanent disability.

Keywords Morbid obesity · Bariatric surgery · Gastric bypass · Copper

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Abbreviations

ASMBS	American Society for Metabolic and Bariatric Surgery
BOMSS	British Obesity and Metabolic Surgery Society
Cu	copper
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RYGB	Roux-en-Y gastric bypass

Introduction

Copper (Cu), a coenzyme in a variety of metalloenzymes, is essential for normal haematopoiesis and nervous system functioning [1]. Its deficiency can lead to haematological disorders commonly anaemia and neutropenia, bone and connective tissue disorders, polyneuropathy, optic neuropathy, and myeloneuropathy. Roux-en-Y gastric bypass (RYGB) is widely regarded as the gold standard bariatric procedure and accounts for approximately 45 % all the bariatric procedures performed worldwide [2]. Morbidly obese patients referred for bariatric surgery can be deficient in a number of micronutrients [3]. When it comes to Cu, up to two-thirds [4] of potential bariatric surgery candidates can be deficient in it. RYGB can further reduce intake as well as absorption of Cu. This has led both the British Obesity and Metabolic Surgery Society (BOMSS) [5] and the American Society for Metabolic and Bariatric Surgery (ASMBS) [6] to recommend a minimum of 2 mg per day of Cu supplementation for patients undergoing RYGB. There is however little evidence in scientific literature to support this recommendation, and

studies comparing adequacy of various doses of Cu supplementation in RYGB patients do not exist.

Patients, who are not routinely supplemented and/or are not concordant with their multivitamins and mineral intake, are at risk of developing Cu deficiency after RYGB. Whilst asymptomatic Cu deficiency is common after RYGB [7, 8], symptomatic deficiency is rare. If not suspected, symptomatic Cu deficiency can be difficult to diagnose and there are reports in literature of patients who have suffered permanent neurological disability because of delays in diagnosis and treatment [9–11].

This has led BOMSS to recommend [5] annual monitoring of serum Cu levels in patients after RYGB. Since RYGB is the commonest bariatric operation in the United Kingdom [12] and the rest of the world [2, 12], this has resource implications. Furthermore, this advice appears to contradict the advice by ASMBS [6] that routine monitoring is unnecessary and that Cu levels should only be evaluated in patients with unexplained anaemia, neutropenia, myeloneuropathy, or impaired wound healing. Apparent contradiction in these guidelines can be confusing for health-care practitioners of metabolic surgery worldwide and formed the basis for this systematic review. We investigated the entire English language scientific literature on copper deficiency after RYGB in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods

An online search of PubMed, MEDLINE, Embase, and Google Scholar was independently carried out by two researchers using keywords like “bariatric surgery,” “gastric bypass,” “Roux en Y Gastric Bypass,” and “Copper” to identify all articles on Cu deficiency in gastric bypass patients. Articles were also identified from references of relevant articles. Last of these searches was carried out on 30 November 2015. Articles reporting Cu deficiency in patients who underwent intestinal bypass (as it is no longer performed by bariatric surgeons) and other gastrointestinal procedures were excluded [13–16], as were those published in non-English language journals [17–19]. Articles on other bariatric procedures were also excluded [20–23]. Articles by Jaiser et al. [24] and Kumar [25] were excluded as these are reviews, and we have included most of the original reports of bariatric cases in these reviews. Studies by Papamargaritis et al. [26] and Halfdanarson et al. [1] were excluded from the systematic review as authors studied a number of bariatric procedures together and did not separately report results with RYGB patients. A total of 22 articles were identified on the subject of Cu deficiency after gastric bypass. Figure 1 gives a PRISMA flow chart for the article selection.

Results

Studies on Symptomatic Cu Deficiency after Gastric Bypass

Table 1 [9–11, 21, 27–39] lists all the reports of symptomatic Cu deficiency after RYGB. There are 17 articles reporting 34 cases of symptomatic Cu deficiency after RYGB in the literature. Out of these, 33 (97 %) were female and the mean age of the patients was 47 years. On average, patients presented 8.6 years after RYGB. Information on supplements was not available for 20 (59 %) patients.

Thirteen out of 34 patients (38 %) were not on any Cu supplement. Only one out of 34 patients was on any multivitamin and mineral supplement; authors do not mention if the supplement contained any Cu. Out of 34 patients, 19 (56 %) presented with neurological symptoms and 17 (50 %) had haematological manifestations. Four out of 19 (21.0 %) patients with neurological complaints presented with optic neuropathy. Anaemia was the dominant haematological manifestation seen in all of the patients with haematological problems. Two out of 17 (11.7 %) patients with haematological disorders had pancytopenia, and a further four (23.5 %) had leucopenia/neutropenia in addition to anaemia.

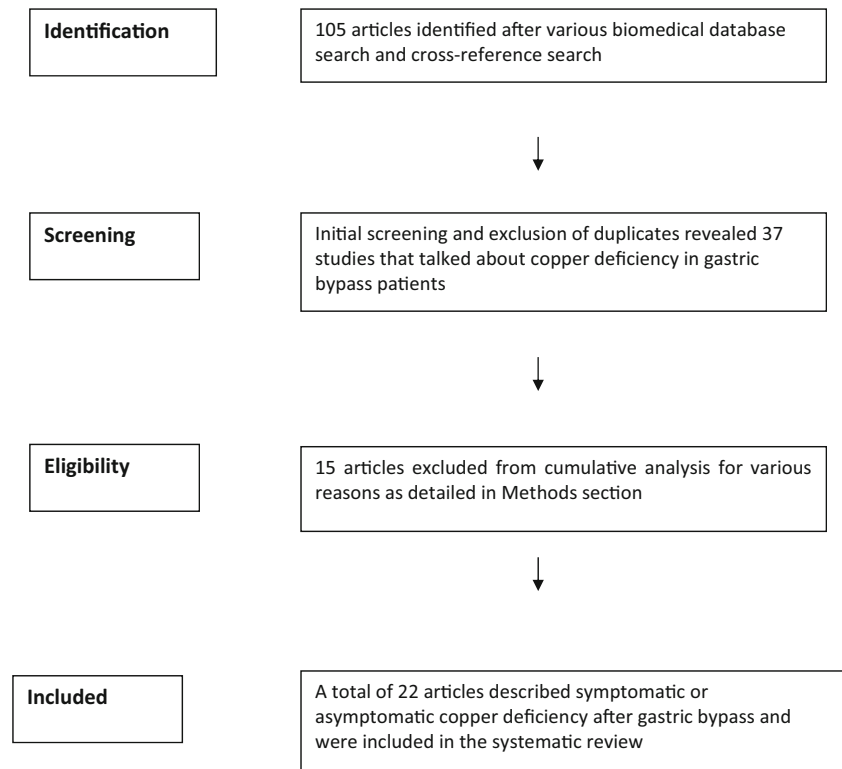
Rapid clinical recovery was observed upon institution of treatment in all 15 out of 17 (88.0 %) patients with haematological disorders this information was available for. This information was not available for the remaining two patients. Eight out of 19 (42.0 %) patients with neurological manifestations in 4 studies were left with residual neurological deficits. Seven out of 19 patients (36.8 %) in 6 studies did not have any residual sequelae. This information was not available for the remaining 4 out of 19 patients.

Studies on Asymptomatic Cu Deficiency after Gastric Bypass

Table 2 [7, 8, 28, 40, 41] includes reports of asymptomatic Cu deficiency after gastric bypass. There are 5 studies reporting on 245 patients with a mean age and BMI of 41 years and 46.1 kg/m², respectively. Out of these, 210 (85.7 %) were females. A total of 23 patients (9.38 %) were diagnosed with Cu deficiency at a mean follow-up of 21.7 months. Though all of the patients in these studies were prescribed a multivitamin and mineral supplement, dose ranged from 0.45 to 3.0 mg. Studies reveal a Cu deficiency rate of 3.8 [40] to 18.8 % [28] at a mean follow-up of 6 months to 5 years.

Discussion

Cu deficiency is rare in the general population because it is abundant in commonly consumed food items like legumes,

Fig. 1 PRISMA flow chart for article selection

potato and potato products, nuts, seeds, beef, and wheat. The recommended daily dietary allowance of 0.9 mg is thus easily met [28, 42]. Bariatric surgery candidates are at higher risk of being deficient in Cu [4]. RYGB can further aggravate Cu deficiency through reduced intake, reduced absorption due to the exclusion of the duodenum and proximal jejunum which are the predominant sites for Cu absorption, or due to excess zinc intake which interferes with copper absorption.

This review shows that approximately 10 % of patients develop asymptomatic Cu deficiency after RYGB. This is to be expected given that majority of the patients in the studies were not prescribed supplements containing the recommended 2.0 mg of Cu. Some authors recommended only 0.45 mg of Cu, which is less than the average daily requirement and significantly below the amounts recommended after RYGB. Others just recommended a multivitamin and mineral supplement without ensuring that the preparations contained Cu in the requisite amount. This is an important point as not all multivitamin and mineral supplements contain Cu and very few contain 2.0 mg of it.

Despite such a relatively high prevalence of asymptomatic Cu deficiency after RYGB, our review shows that only 34 symptomatic cases have been published in English language scientific literature with clear signs and symptoms attributable to Cu deficiency after RYGB. Interestingly, only one of these patients was documented to be on a supplement and even for this patient, we do not know the exact amount of Cu in the tablet.

Despite almost a complete lack of knowledge regarding routine Cu supplementation and early detection of symptomatic Cu deficiency after RYGB in the past, the literature has recorded very few patients with residual neurological deficits. We believe the incidence of neurological problems can be further reduced if clinicians focused on ensuring their patients were adequately supplemented with multivitamin/mineral tablets containing at least 2.0 mg of Cu. Papamargaritis et al. [26] found a 2.0 % Cu deficiency in patients prior to bariatric surgery and a 0–5 % deficiency rates after surgery. Patients were supplemented with a daily multivitamin and mineral tablet containing 2 mg of Cu, and importantly, the authors did not find any significant change in median serum Cu concentration during follow-up. In this study of 437 patients, 57 % patients underwent RYGB; the remaining underwent sleeve gastrectomy and gastric banding. Authors concluded that patients concordant with multivitamins and mineral supplements maintained normal Cu concentration during the first years after bariatric surgery. Since the calorie intake after surgery increases with passage of time and the bowel undergoes hypertrophy and adaptation, one can also expect copper levels to remain in the normal range in the longer term for well-supplemented patients.

Given such a low frequency of symptomatic Cu deficiency, routine lifelong screening may not be justified for all patients undergoing RYGB and can be reserved for high-risk and clinically symptomatic patients. Routine screening does not come without its own problems. Apart from the obvious cost

Table 1 Reports of symptomatic copper deficiency after Roux-en-Y gastric bypass

Author	Supplement	Time after surgery	Patients with copper deficiency	Clinical symptoms	Final clinical outcome
Griffith et al. [27] Mean age: 55.5 Females: 2 Study type: case report Evidence level: level 5	No copper supplement	21 years	2	Anaemia, neutropenia, gait disturbances	Complete haematological recovery but partial neurological recovery
Gletsu-Miller et al. [28] Mean age: 44.2 Females: 13 Study type: cohort study Evidence level: level 3	NA	0–5 years	13	Anaemia (46 %), leucopenia (15 %), fatigue (38 %), various neuropathies (38 %)	Equally prevalent within the first year, within years 1–3 or within years 3–5
Shah et al. [29] Age: 35 Female Study type: case report Evidence level: level 5	NA	36 months	1	Optic neuropathy	Complete recovery
Yarandi et al. [30] Age: 47 Female Study type: case report Evidence level: level 5	None	13 years	1	Anaemia, neutropenia, myelopathy, optic neuropathy	Residual neurological disability and visual loss
Robinson et al. [31] Age: 51 Female Study type: case report Evidence level: level 5	One multivitamin	20 years	1	Pancytopenia	Complete recovery
Naismith et al. [32] Age: 55 Female Study type: case report Evidence level: Level 5	None	22 years	1	Bilateral optic neuropathy leading to blindness, progressive myeloneuropathy, anaemia, leucopenia	NA
Choi et al. [33] Age: 45 Female Study type: case report Evidence level: level 5	None	6 years	1	Myeloneuropathy	Complete recovery at 18 months
Pineles et al. [11] Age: 42 Female Study type: case report Evidence level: level 5	None	>20 years	1	Optic neuropathy, myelopathy	Left with residual disabilities
Khambatta et al. [34] Age: 38 Female Study type: case report Evidence level: level 5	None	16 years	1	Anaemia, neurologic symptoms	NA
O'Donnell et al. [35] Age: 60 Male Study type: case report Evidence level: level 5	NA	14 months	1	Neurological symptoms, anaemia	Complete recovery
Rounis et al. [10] Age: 33 Female Study type: case report Evidence level: level 5	None	5 months	1	Neurological symptoms	Significant recovery but left with some residual disabilities
Shahidzadeh et al. [36] Age: 62 Female Study type: case report Evidence level: level 5	None	13 years	1	Neurological symptoms, anaemia	“Dramatic improvement” but not clear if any residual disability

Table 1 (continued)

Author	Supplement	Time after surgery	Patients with copper deficiency	Clinical symptoms	Final clinical outcome
Goldberg et al. [37] Age: 38 Female Study type: case report Evidence level: level 5	None	7 years	1	Myelopathy	NA
Sonu et al. [38] Age: 66 Female Study type: case report Evidence level: level 5	None	NA	1	Pancytopenia	Treatment resulted in resolution of pancytopenia
Kumar et al. [21] Age: 64 Female Study type: case report Evidence level: level 5	None	12 years	1	Myelopathy, anaemia (patient also receiving Zn supplement without Cu)	NA
Chai et al. [39] Age: 58 Female Study type: case report Evidence level: level 5	None	NA	1	Myeloneuropathy	Complete symptomatic recovery
Juhasz-Poscine [9] Mean age: 46 Female: 5 (100 %) Study type: case series Evidence level: level 4	NA	9.2 years	5	Myelopathy	All improved and some improved considerably. It would seem all were left with some residual disability

NA not available

implications, diagnosis of clinically insignificant biochemical abnormalities can potentially result in unnecessary patient anxiety. Currently, bariatric surgery patients are required to undergo lifelong screening blood tests for early detection of a number of micronutrient deficiencies. A complete risk-vs-benefit evaluation, including a cost analysis, has not been performed for the vast majority of these investigations. Majority of these asymptomatic laboratory abnormalities may not necessarily result in any clinical harm.

This review supports that there is a definite prevalence of Cu deficiency after RYGB. It would hence seem prudent that patients are advised to take a multivitamin and mineral tablet containing 2 mg of Cu per day after bariatric surgery, as has been recommended by both British [5] and American guidelines [6], at least until comparative studies examining various supplement doses become available. Since zinc can interfere with Cu absorption, it is recommended that patients on zinc supplements are also supplemented with Cu (1 mg Cu for 8–5 mg zinc) [5]. It is important to note in this context that not all multivitamin and mineral preparations contain the required amount of Cu or indeed any at all.

Most patients with clinical Cu deficiency after RYGB can be adequately treated with timely diagnosis and treatment. It is hence crucial that health-care professionals consider measuring Cu levels in patients with anaemia, neutropenia,

myeloneuropathy, or impaired wound healing. Patients should also be advised to report any neurological symptoms early to avoid irreversible damage. Patients at high risk of copper deficiency, e.g. those with established neurological deficits, non-compliance to vitamin and mineral supplements, pregnant and lactating women, patients with prolonged severe diarrhoea or vomiting, prolonged zinc supplement intake, alcoholics, and those with previous history of copper deficiency requiring hospitalization, should undergo a careful haematological and neurological assessment backed by monitoring of copper levels as and when clinically indicated. It is also worth bearing in mind in this context that in clinical practice diagnosis of clinical Cu deficiency can only be made when deficiencies of other micronutrient like iron, vitamin B₁₂, and thiamine have either been ruled out or corrected. Furthermore, though rare after RYGB, patients after malabsorptive bariatric procedures may harbour multiple co-existing micronutrient deficiencies leading to complex clinical presentations. It would seem prudent to take an opinion from a dedicated bariatric physician or chemical pathologist for such patients.

There are several weaknesses to this review. Most of the studies in this review are either case reports or cohort studies. This limits the conclusion that can be reached from this review. Future studies need to determine the prevalence of symptomatic Cu deficiency in adequately supplemented

Table 2 Studies on copper deficiency after Roux-en-Y gastric bypass on asymptomatic patients

Author	Supplement	Time after surgery	Patients with copper deficiency	Comments
Balsa et al. [40] Number: 52 Mean age: 45.36 years Females: 48 (92.3 %) Mean BMI: 46.2 BMI at diagnosis: 34.11 Study type: cohort study Evidence level: level 3	Multivitamin/mineral containing 0.9 mg of elemental Cu daily	5 years	2 (3.8 %)	- None of the patients were deficient in Cu at the baseline
Rojas et al. [41] Number: 63 Mean age: 36.9 years Females: 63 (100 %) Initial BMI: 43.8 kg/m ² BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	Received multivitamin/mineral supplement containing 0.9–3.0 mg Cu (<i>n</i> = 20, 0.9 mg; <i>n</i> = 20, 1.0 mg; <i>n</i> = 23, 3.0 mg)	6 months	3 (5 %)	- None of the patients were deficient in Cu before surgery - Cu levels were significantly lower at 6 months compared to before surgery (<i>p</i> < 0.001)
Ernst et al. [7] Number: 78 Mean age: 45.8 years Females: 56 (71.8 %) Initial BMI: 48.2 kg/m ² Final BMI: 31.1 kg/m ² Study type: controlled study Evidence level: level 2	Multivitamin/mineral supplement containing 0.45 mg of Cu per day	1.3 years	12 (15.4 %)	- Serum Cu levels significantly lower in the RYGB group vs obese controls - None of the obese control were deficient in Cu vs 15.4 % of patients in the RYGB group (<i>p</i> < 0.001)
Gobato et al. [8] Number: 36 Age: 37.66 years Females: 27 (75 %) Initial BMI: 44.2 BMI at diagnosis: 28.49 Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement (Centrum [®] which contains 2.0 mg Cu)	6 months	3 (8.3 %)	Cu deficiency was absent before surgery. 26 patients were supplemented preoperatively too
Gletsu-Miller et al. [28] Number: 16 Mean age: 33.1 years Females: 16 (100 %) Initial BMI: 49.0 Final BMI: 31.6 Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement (Cu amount not specified but probably <1.0 mg, see comment)	24 months	3 (18.8 %)	- Patients who had Cu deficiency also had lower haemoglobin and ferritin - Total combined Cu intake from food and supplements was 1.0 mg in 10 patients at 24 months

patients as well as the ideal supplemental dose in RYGB patients. This review specifically examines RYGB patients only, and results cannot hence be extrapolated to other bariatric procedures. It is though likely that patients undergoing sleeve gastrectomy or gastric band will be at a lesser risk of developing Cu deficiency.

Conclusion

Approximately 10 % of patients can be deficient in Cu after RYGB, but symptomatic deficiency is rare. Clinically manifested Cu deficiency can be easily and

completely corrected if diagnosis is suspected early; delays however, may result in permanent neurological deficits. Routine monitoring of Cu levels is probably unnecessary after RYGB. Clinicians should instead focus on supplementing their patients with daily multivitamin and mineral tablets containing at least 2.0 mg of copper and target their investigations to patients with unexplained haematological or neurological abnormalities. High-risk patients should undergo a careful haematological and neurological assessment with a low threshold for copper level monitoring.

Authors' Contributions KM conceived the idea for the topic. PK, KM, NH independently collected information and analysed it. All authors

participated in discussions on the topic and manuscript writing. All authors have seen the final version and approve of it.

Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent Not applicable

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