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REVIEW ARTICLE

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

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Abstract Up to 50% of patients have zinc deficiency before bariatric surgery. Roux-en-Y gastric bypass (RYGB) is the commonest bariatric procedure worldwide. It can further exacerbate zinc deficiency by reducing intake as well as absorption. The British Obesity and Metabolic Surgery Society, therefore, recommends that zinc level should be monitored routinely following gastric bypass. However, the American guidance does not recommend such monitoring for all RYGB patients and reserves it for patients with 'specific findings'. This review concludes that clinically relevant Zn deficiency is rare after RYGB. Routine monitoring of zinc levels is hence unnecessary for asymptomatic patients after RYGB and should be reserved for patients with skin lesions, hair loss, pica, dysgeusia, hypogonadism or erectile dysfunction in male patients, and unexplained iron deficiency anaemia.

Keywords Morbid obesity · Bariatric surgery · Gastric bypass · Zinc

Abbreviations

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

Introduction

Zinc (Zn) is an essential mineral, which plays a key role in a number of cellular metabolic processes. It plays a role in DNA synthesis, cell division, wound healing, immune functioning, and protein synthesis. More than 300 enzymes and >1000 transcription factors require Zn for their activity [1]. Its deficiency can lead to hair loss, diarrhoea, glossitis, nail dystrophy, hypogonadism in males, impotence, taste alteration, delayed wound healing, eye and skin lesions, and acrodermatitis enteropathica [2–5]. It can also be a cause of unexplained anaemia after gastric bypass and should be considered when routine screening for iron deficiency anaemia is negative [5, 6].

Roux-en-Y gastric bypass (RYGB) is the commonest bariatric procedure worldwide [7] and in the UK [8]. Up to half [9–13] of bariatric surgery patients are deficient in Zn preoperatively and RYGB can further exacerbate it [4, 9, 12] through probably both reduced intake [14–17] and reduced absorption [14, 18] as Zn is predominantly absorbed in the duodenum and the proximal jejunum.

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Both the British Obesity and Metabolic Surgery Society (BOMSS) [5] and the American Society for Metabolic and Bariatric Surgery (ASMBS) [6] recommend Zn supplementation after RYGB. Though these guidelines do not specify the exact dose of such Zn supplementation after RYGB, it is suggested that a multivitamin/mineral formulation containing 8–15 mg of Zn for every milligram of copper (Cu) should be sufficient. Since these guidelines further recommend 2 mg of elemental Cu daily after RYGB, it must imply 16–30 mg of elemental Zn daily in these supplements. A number of Zn salts or chelated Zinc preparations with varying bioavailability are used in the supplements. Sulphate, oxide, and gluconate are some of the commonly used ones. There is little research on the type of the salt that should be used in the supplements.

Freeland-Graves et al. [19] showed in their systematic review and meta-analysis that Zn levels decrease after bariatric surgery (they examined levels at 6 months after surgery) but a number of studies in this meta-analysis were on procedures other than RYGB and it cannot hence be an adequate representation of what happens to Zn levels after RYGB. Moreover, it is not clear from this review whether patients were supplemented and the dose of Zn if they were, as that will have an obvious implication on Zn levels after surgery.

Patients not supplemented adequately or those who are non-compliant with their supplements are at obvious risk of developing Zn deficiency after RYGB. This is probably what has led BOMSS to recommend annual monitoring of Zn levels after RYGB [5], a recommendation not shared by ASMBS [6]. ASMBS only recommends evaluation of Zn levels in patients with 'specific findings'. It further states that Zn deficiency should be 'considered in patients with hair loss, pica, significant dysgeusia, or in male patients with hypogonadism or erectile dysfunction'.

The apparent contradiction in these guidelines can cause confusion and formed the basis for this systematic review. We investigated the entire English language scientific literature on Zn deficiency after RYGB in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods

An online search of PubMed was carried out using keywords like 'bariatric surgery', 'gastric bypass', 'Roux en Y Gastric Bypass', 'Zinc', and 'Zn' to identify all articles on Zn deficiency in RYGB patients. Articles were also identified from references of relevant articles. Last of these searches was carried out on 27th July' 2016.

We excluded articles describing Zn deficiency in procedures other than RYGB as well as those where authors described Zn levels after a range of bariatric procedures together and not just after RYGB separately [9], those on distal gastric bypass [20], and those in languages other than English [21].

A total of 19 articles were identified on the subject of Zn deficiency after gastric bypass. Figure 1 gives a PRISMA flow chart for article selection.

Results

Studies on Symptomatic Zn Deficiency after Gastric Bypass

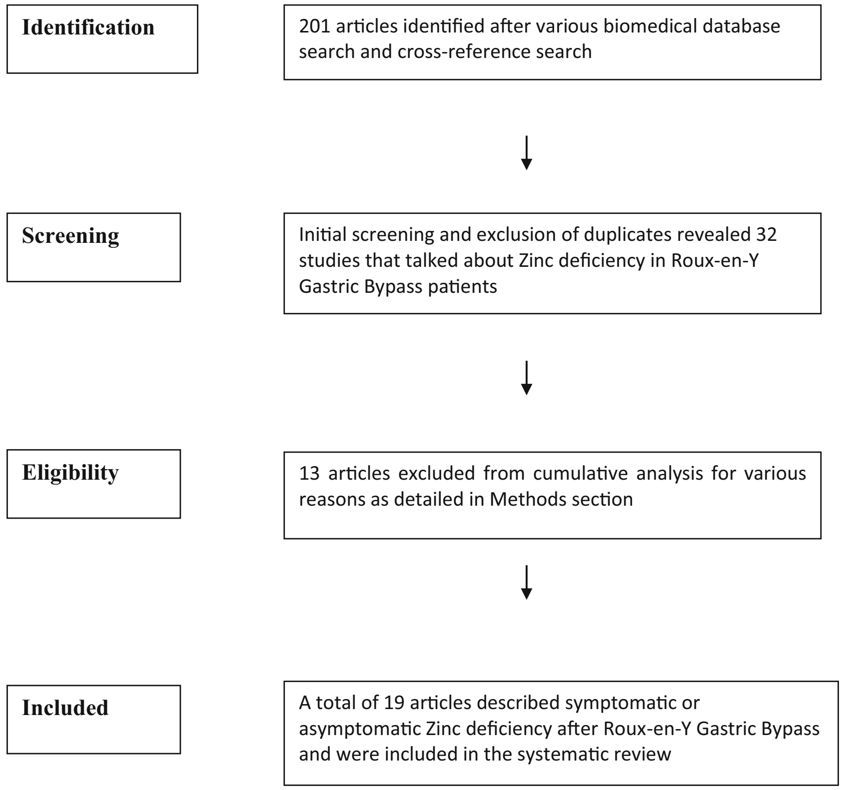
Table 1 [22–27] lists all the reports of symptomatic Zn deficiency after RYGB. The scientific literature contains only six articles reporting six cases of symptomatic Zn deficiency after RYGB. Out of these, 4 (67%) were female and the mean age of the patients was 44.5 years. On average, patients presented 6 (2–10) years after RYGB. Information on supplements was not available for 4 (67%) patients. One patient (16%) had stopped her supplement and only one (16%) was clearly documented to be on a multivitamin supplement. Even for this patient, the amount of Zn in the tablet was not clearly stated. All six (100%) patients presented with a skin rash. One patient (16%) also suffered from diarrhoea at presentation.

Oral Zn led to resolution of symptoms in 5/6 (83.3%) in 1–4 weeks. Two of these five patients were given 220 mg Zn sulphate containing 50 mg elemental Zn daily. One (16%) patient did not respond to oral treatment and needed the intravenous supplement. This patient was given 35 mg Zn daily.

Studies on Asymptomatic Zn Deficiency after Gastric Bypass

Table 2 [12, 14, 17, 28–37] includes reports of asymptomatic Zn deficiency after gastric bypass. There are 13 studies reporting on 1469 patients with a mean age and BMI of 43.2 years and 46.5 kg/m^2, respectively. Out of these, 1026/1283 (79.9%) were females. A total of 351 patients (23.9%) were diagnosed with Zn deficiency at a mean follow-up of 29.5 months. Though patients in 12/13 of the studies in this review (not prescribed in 1 study; n = 24/1469; 1.6%) were prescribed a multivitamin/mineral supplement, dose was unclear in 2 studies (n = 221/1469; 15.0%). In the remaining 10 studies (n = 1224/1469; 83.3%), the dose of Zn supplement ranged from 7.5 to 25.0 mg. Studies revealed a Zn deficiency rate of 6.35% (30 AA) to 68.0% [17] at a follow-up of 2 months to 5 years. The highest rate of 68.0% was seen in the patients [17] who were not given any Zn supplement.

Fig. 1 PRISMA flow chart for article selection



Discussion

Animal proteins, particularly red meat and poultry, are excellent sources of Zn. Dairy products, nuts, whole grains, legumes, and yeast are other good sources. On the contrary, fruits and vegetables are not good sources and therefore low protein diets and vegetarian diets are poor in Zn. Fibre and phytate in the vegetarian food can further reduce Zn absorption by binding to it whereas animal protein enhances the absorption of Zn contained in the plant food by binding to the phytates as well as releasing amino acids that keep Zn in solution [38].

Zn is predominantly absorbed in the duodenum and the jejunum by a carrier-mediated mechanism where it competes with other metals (like Cu and iron) for absorption. Though under normal circumstances the absorptive capacity is not saturated, there is a potential for it in post RYGB patients as a result of decreased absorptive capacity and multiple supplements. It hence makes sense that these patients avoid taking iron and Zn supplements at the same time. Since Zn and Cu are typically consumed together, it is important to maintain the suggested ratio of 1 mg Cu per 8–15 mg Zn to maintain a balance. The overall effect of calcium on Zn absorption is not entirely clear and probably insignificant. There is further evidence that consumption of animal protein enhances Zn absorption.

Serum Zn represents about 0.1% of the whole body Zn and about 70.0% of it is bound to the albumin. It is used by almost every single human cell for a range of metabolic processes. Zinc is lost from the body through the gut, kidneys, and the skin [38].

The fact that there are only six published reports of symptomatic Zn deficiency after RYGB when hundreds of thousands of this operation have been carried out worldwide might indicate that it is a rare condition. Moreover, every single one of these patients made full recovery upon diagnosis and treatment and no patient suffered any permanent harm as a result of Zn deficiency.

As we have discussed before, Zn deficiency is not uncommon in patients seeking bariatric surgery. There is currently no recommendation that morbidly obese in the community undergo routine screening for Zn deficiency. Given the fact that any clinical relevant Zn deficiency can be diagnosed and treated with relative ease, it would indeed be difficult to make a case for such routine screening.

It is also evident that RYGB leads to not just a reduction in intake of Zn [14, 15] but also its absorption [14, 18]. In the study by Ruz et al. [14], dietary Zn intake was 9.1, 5.4, 6.4, and 7.2 mg/d before and 6, 12, and 18 months respectively after RYGB. Pires et al. [15] found patients were consuming lower amount of Zn than required 6 months after surgery. Mean intake in males was 8.2 mg as opposed to recommended intake of 9.4 mg and in females was 6.3 mg as opposed to 6.8 mg, respectively.

Rosa et al. [18] found significantly reduced serum Zn levels 3 months after RYGB to an oral test dose of Zn with

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

Author	Supplement	Time after surgery	Patients with zinc deficiency	Clinical symptoms	Final clinical outcome
Monshi et al. [22] Mean age: 29 years Female Study type: case report Evidence level: level 5	NA	7 years	1	Skin rash	Complete resolution of rash within a week
Mankaney et al. [23] Age: 54.0 years Female Study type: case report Evidence level: level 5	Had stopped her multivitamin/mineral supplement a few months ago	8 years	1	Skin rash	Nearly complete resolution of rash in 4 weeks
Vick et al. [24] Age; 38.0 years Female Study type: case report Evidence level: level 5	On multivitamin/mineral supplement (Zn dose not clear)	10 years	1	Skin rash	Failure with oral (35 mg daily) supplementation. Needed intravenous Zn supplementation
Shahsavari et al. [25] Age: 39.0 years Male Study type: case report Evidence level: level 5	NA. Concomitant alcohol abuse	6 years	1	Skin rash, Diarrhoea	Rash improved on 220 mg Zn Sulphate daily orally
Zouridaki et al. [26] Age: 45.0 years Female Study type: case Report evidence level: level 5	NA	2 years	1	Skin rash	Zinc supplementation led to dramatic recovery of symptoms
Bae-Harboe et al. [27] Age: 62.0 years Male Study type: case report Evidence level: level 5	NA	3 years	1	Skin rash	Serum Zn was normal Supplementation with Zn Sulphate 220 mg/day led to near resolution of hand dermatitis in 6 days

NA not available

an 89% reduction in the serum Zn curve. Authors suggested that this indicated an impairment in Zn absorption after RYGB. Ruz [14] et al. confirmed that 'Zn absorption capacity is significantly impaired soon after RYGB and this persists at least until 18 months after surgery. In this study, percentage Zn absorption decreased from 32.3% before surgery to 13.6% by 6 months after surgery.

It is hence sensible that patients are advised routine Zn supplementation after RYGB. Though both ASMBS and the BOMSS support this recommendation, they do not mention the exact dose of Zn that should be recommended for patients after RYGB. As we lay out in the Introduction section, it cannot be above 30 mg of Zn to comply with the recommendation from these bodies that patients take 2 mg of Cu daily after RYGB. It is also worth examining in this context if over-supplementation can lead to Zn toxicity.

Zn toxicity is rare and the safe upper limit for daily Zn intake is 40 mg (including dietary and supplemental Zn) for both adult males and females [2, 39]. It would hence appear that we could safely recommend up to 30 mg Zn daily lifelong for these patients without any significant risk of Zn toxicity or Cu deficiency. It is interesting as most of the studies reporting on asymptomatic Zn deficiencies have evaluated Zn levels in patients taking much less than this amount of Zn daily. For example, Ruz et al. [14] concluded that a supplement of 9.5 mg Zn daily after RYGB would not be sufficient to prevent an impairment of Zn status. Authors suggested that there was hence the justification for use of a higher dose of supplement probably in the range of 40–60 mg/day. However, in view of the potential for toxicity at doses above >40 mg/day and a potential for interference with absorption of other trace elements like Cu and iron, it might not be prudent to recommend such excessive amounts of Zn.

Homan et al. [37] compared Zn status in three different patient groups: the first one on an enriched multivitamins tablet containing 22.5 mg of Zn, the second group on a standard multivitamin (amount of Zn not clear), and the third not taking any supplements. After 36 months, none of the patients (0/52) in enriched multivitamin group (group 1) became deficient compared to 8.0% (n = 3/37) in the standard multivitamin group (group 2) and 27.0% (n = 6/22) amongst those not on any supplement (group 3). The difference between group 1 and other groups was statistically significant. At the same

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

Author	Supplement	Time after surgery	Patients with zinc deficiency	Comments
Balsa et al. [28] 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 8 mg of elemental Zn daily	5 year	11 (21.2%)	—The average serum Zn level did not change during the follow-up in these patients. —9/11 patients at 5 years with hypozincaemia had longer alimentary and biliopancreatic limbs. —The mean serum Zn level was significantly lower in the longer limb RYGB patients from 24 months onwards until the end of the study period at 60 months.
Rojas et al. [29] 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 7.5 mg Zn (n = 20), 15 mg Zn (n = 20), and 25 mg Zn (n = 23)	6 months	4 (6.35%)	—Dietary intake of Zn decreased significantly after surgery 5.6 vs 9.6 mg daily) —Plasma and hair Zn concentration increased after surgery. —Number of patients with low plasma Zn remained unchanged at two and that with low hair Zn decreased from six to four. —The type of supplementation had no effect on Zn levels
Gobato et al. [12] Number: 36 Age: 37.66 Females: 27 (75%) Initial BMI: 44.2 BMI at diagnosis: 28.49 Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement daily (Centrum ® containing 15 mg Zn). 26 patients received it daily for 3 months before surgery.	6 months	22 (61.1%)	55.5% were deficient in Zn preoperatively and 61.1% postoperatively. (p = 0.54)
Gasteyger et al. [30] Number: 137 Age: 39.9 Females: 110 (80.2%) Initial BMI: 46.7 BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement containing 8 mg Zn prescribed from 1 to 6 months after surgery	24 months	17 (12.0%)	NA
Gong et al. [31] Number: 121 Age: 46.0 Females: 81 (67%) Initial BMI: 47.0 BMI at Diagnosis: 33.8 Study type: cohort study Evidence level: level 3	Multivitamin/mineral daily (amount of Zn unclear)	6 months	17/ 87 (20%) at 6 months	The mean serum Zn for the cohort was normal at 6, 12, and 24 months after surgery
Ruz et al. [14] Number: 67 Mean age: 36.9 years Females: 67 Initial BMI: 45.2 kg/m^2 BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	Patients were randomized to one of the two multivitamin/mineral supplements. The first group (n = 36) received 7.5 mg Zn and the second group (n = 31) 15 mg Zn	18 months	12/ 56 (21.4%) patients had low plasma Zn at 18 months	—4.5% patients were deficient in Zn preoperatively —There was no difference in any of the Zn status indicators in either group. —Of the 5 indexes of zinc status, 3 (plasma zinc, erythrocyte membrane alkaline phosphatase activity, and exchangeable Zn pool) were significantly lower 12 or 18 months after RYGB.
Cominetti et al. [17] Number: 24	No supplement given	2 months	16 (68.0%)	—Preoperatively 71.0% patients had low plasma Zn concentration

Table 2 (continued)

Author	Supplement	Time after surgery	Patients with zinc deficiency	Comments
Mean age: 37.0 years Females: 20 (83.3%) Initial BMI: 43.6 kg/m^2 BMI at diagnosis: 36.8 Study type: cohort study Evidence level: level 3				—The mean dietary Zn intake came down to 6.7 from 10.5 mg/day preoperatively ($p < 0.08$)
Sallé et al. [32] Number: 266 Mean age: 43.0 years Females: 223 (83.8%)) Initial BMI: 45.0 kg/m^2 BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	—Multivitamin/mineral Supplement containing 15 mg Zn —Patients were given additional Zn supplements as needed.	24 months	93 (34.8%) at 24 months	—8.1% patients were deficient in Zn preoperatively. Zn deficiency was significantly more frequent post surgery —Plasma Zn concentration decreased significantly from 6 to 12 months after surgery and then remained stable from 12 to 24 months
Gehrer et al. [33] Number: 86 Mean age: NA Sex: NA Initial BMI: NA BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement containing 10 mg Zn	24 months	32 (37.0%)	14.0% patients had Zn deficiency preoperatively
Dalcanale et al. [34] Number: 75 Mean age: 49.3 years Females: 67 (89.3) Initial BMI: 56.5 kg/m^2 BMI at diagnosis: 29.4 kg/m^2 Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement containing a mean of approximately 20.4–23.0 mg Zn at different time periods	24 months	30 (40.5%)	—Mean serum Zn level did not change significantly surgery. —Authors did not provide numbers for preoperative Zn deficiency rates
Madan et al. [35] Number: 100 Mean age: NA Sex: NA Initial BMI: NA BMI at diagnosis: NA Study type: cohort study Evidence level: level 3	Multivitamin/mineral supplement daily (amount of Zn unclear)	1.0 year	12/33(36.0%)	28.0% patients were deficient preoperatively
Moizé et al. [36] Number: 294 Mean age: 45.2 years Females: 226 (77.0%) Initial BMI: 47.4 kg/m^2 Final BMI: NA Study type: comparative study Evidence level: level 3	Multivitamin/mineral supplement containing 8.0 mg Zn per day	5.0 years	76 (25.7%)	11.5% Zn deficiency preoperatively
Homan et al. [37] Number: 148 Mean Age: 44.5 years Females: 95 (64.1%) Initial BMI: 44.7 kg/m^2 Final BMI: NA (EWL 74.0%) Study type: comparative study Evidence level: level 3	63 patients on an enhanced multivitamin/mineral preparation (containing 22.5 mg Zn) daily, 57 patients were on a standard multivitamin (amount of Zn unclear) and 28 patients were on no supplement	3.0 years	9/111 (8.0%)	—None of the patients in the enriched formulation were deficient in Zn compared to 3 (8.0%) in the standard multivitamin/mineral group and 6 (27.0%) in the patients on no supplements —Mean serum Zn concentration was equal in the enriched and the standard supplement

time, the mean serum concentration was not different between group 1 and group 2.

This review shows that asymptomatic Zn deficiency is common in patients supplemented with 7.5–25 mg Zn daily. At the same time, it would appear that patients on a higher dose of Zn [37] are less likely to become deficient in Zn. There is no study in scientific literature yet examining routine supplementation with 30 mg Zn daily in these patients. Indeed, there is a scarcity of studies examining different doses of Zn supplement [14, 37]. The optimum dose of Zn supplementation in RYGB patients does indeed remain to be determined but will probably have to be higher than what has been examined thus far.

Zn status is difficult to measure [14] due to its widespread distribution as a component of various proteins and nucleic acids. Plasma or serum Zn levels are the most commonly used indices for evaluating Zn deficiency but the test suffers from both poor sensitivity and specificity [3, 27, 40]. These levels may not accurately reflect cellular Zn status due to efficient homeostatic control mechanisms [2]. Clinically, symptomatic Zn deficiency may be present in absence of abnormal serum levels. A diagnosis of Zn deficiency hence requires a combination of clinical picture and biochemical tests for accuracy. Routine monitoring of Zn levels after RYGB will hence potentially result in over treatment as the vast majority of patients with asymptomatic Zn deficiency as determined by plasma Zn levels may never come to any harm. It is worth noting here that patients who have undergone RYGB constitute a high-risk group for Zn deficiency and the condition should be suspected in patients presenting with signs and symptoms of Zn deficiency as outlined before.

Though some authors [40] have suggested that the estimates of Zn deficiency can be improved by measurement of Zn in erythrocytes and hair or by measuring activities of enzymes dependent on Zn, others [14, 15] have found that erythrocyte Zn levels may behave erratically and may actually increase [15] or remain unchanged [14] with a concomitant fall in serum and urinary Zn levels. Similarly, Ruz et al. [14] found hair Zn to be higher at 6 and 12 months after RYGB compared to preoperative values. Authors reported that the findings were 'contrary to expectations' and may be linked to the use of Zn-containing shampoo. Lowe et al. [41] concluded from a recent review of the tools that can be used to biochemically diagnose Zn deficiency that plasma Zn was the best tool.

Given that symptomatic Zn deficiency is rare, routine lifelong screening for Zn status may not be justified for all patients undergoing RYGB. The problem is further compounded by the lack of a biochemical test with a high level of sensitivity and specificity. Apart from the obvious cost implications, diagnosis of clinically insignificant biochemical abnormalities can cause unnecessary patient anxiety. The majority of these asymptomatic Zn deficiencies may not necessarily result in any clinical harm.

At the same time, this review supports that there is a definite prevalence of Zn deficiency after RYGB and it is hence worth recommending lifelong daily Zn supplement for these patients. There is currently no consensus on the optimum dose of Zn for these patients and future studies need to examine the safety and efficacy of our suggested dose of 30 mg Zn daily.

There are several weaknesses to this review. First of all, due to publication bias, we cannot be confident that there have not been more cases of clinically symptomatic Zn deficiency after RYGB. Authors accept that the published literature seems to underrepresent the burden of the problem and there is a significant potential for type 2 error in this review. It is further possible that there are reports of Zn deficiency cases buried in dermatology literature that we have not been able to identify using our search strategy. Moreover, this review focuses on RYGB and is not qualified to comment on other bariatric procedures. One can though reasonably expect it to be less of a problem with gastric band or sleeve gastrectomy. With same supplementation protocol, Moizé et al. [36] found Zn deficiency to be 25.7% in RYGB group compared to 12.5% in the sleeve group at 5 years (preoperatively 11.5 and 8.1%, respectively).

Conclusion

Symptomatic Zn deficiency is rare and easily corrected with oral Zn supplementation. Routine monitoring of Zn levels is hence unnecessary after RYGB in adequately supplemented patients. Though there is currently no clear consensus regarding the optimum dose of Zn supplement in these patients, we suspect a dose of approximately 30 mg daily will probably deliver maximum efficacy at minimal risk.

Authors' Contributions KM conceived the idea for the topic, performed the review, and wrote most of the manuscript. AB and VB critically reviewed the manuscript. All authors participated in discussions on the topic and contributed to manuscript writing. All authors have seen the final version and approve it.

Compliance with Ethical Standards

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

Statement of Human and Animal Rights Statement of human and animal rights is not applicable in this study.

Statement of Informed Consent Statement of informed consent is not applicable in this study.

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