




Vitamin and Mineral Deficiency 12 Years After Roux-en-Y Gastric Bypass a Cross-Sectional Multicenter Study

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Received: 4 April 2023 / Revised: 10 August 2023 / Accepted: 10 August 2023 / Published online: 27 August 2023
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Abstract

Purpose Micronutrient deficiencies are common after Roux-en-Y gastric bypass (RYGB). This study explores whether vitamin and mineral deficiency was associated with adherence to recommended supplementation 12 years after RYGB.

Materials and Methods The cross-sectional Bariatric Surgery Observation Study (BAROBS) was conducted in 2018–2020 at three hospitals in Central Norway. We report data on 490 patients' self-reported adherence to recommended supplements and vitamin and mineral levels in the blood. The patients, who had RYGB between 2003 and 2009, were recommended an over-the-counter multivitamin-mineral supplement, calcium/vitamin D (1000 mg/20 µg) and vitamin B₁₂ injections (reimbursed), since bariatric supplements were not available then.

Results Mean (SD) age was 40.1 ± 9 years at RYGB, and time to follow-up 11.7 ± 1.6 years. Of 490 patients, 393 (80%) were women. Among 361 (74%) patients' adherent to multivitamin-mineral supplements; folate, vitamin B₂, and vitamin B₆ deficiency were present in 39 (11%), 103 (29%), and 63 (17%) patients, respectively. The same deficiencies occurred in 44 (34%), 67 (52%), and 67 (52%) patients' non-adherent to recommendations. Although 466 (95%) patients reported adherence to vitamin B₁₂ supplements, sub-optimal levels were found in 73 (16%) patients.

Though 336 (69%) patients adhered to calcium/vitamin D supplements (1000 mg/20 µg), sub-optimal vitamin D levels (< 75 nmol/l) were found in 174/336 (52%) adherent patients and 120/154 (78%) non-adherent patients.

Conclusion Twelve years after RYGB, adherence to supplements, though in sub-optimal doses of new recommendations, decreases the probability of vitamin and mineral deficiency, especially for thiamine, vitamin B₂, vitamin B₆, folate, vitamin B₁₂, and vitamin D, but does not eliminate it.

Keywords Gastric Bypass · Vitamin and mineral deficiency · Long-term follow-up · Vitamin D · Vitamin B₁₂

Key Points

- 74% take recommended multivitamin-mineral supplement 12 years after RYGB surgery.
- Few patients' adherent to calcium with vitamin D reached optimal vitamin D levels.
- Adherence to calcium/vitamin D triples the odds of having optimal vitamin D.
- Adherence to multivitamin supplements leads to five times more likely normal B₆.

Extended author information available on the last page of the article

Introduction

Background

Roux-en-Y gastric bypass (RYGB) for treating severe obesity leads to reduced uptake of vitamins and minerals from food, as the duodenum, the most important area for absorption of micronutrients, is bypassed [1, 2]. The most commonly reported nutritional deficiencies after bariatric surgery are iron,

folate, vitamin B₁₂, copper, zinc, calcium, and vitamin D [1, 3]. The guidelines for supplementation after bariatric surgery aim to give simple recommendations which should be easy and affordable for all patients and give a reasonable balance between benefits and side effects [4, 5]. Former studies have found prevalence of micronutrient deficiency in patients without supplementation after obesity surgery that ranges from 15 to 38% in folic acid, 37–50% in vitamin B₁₂ and 47–66% for iron and vitamin D from 20 to 80% related to geographical areas [6]. A Norwegian study from 2015 found that 70% of the patients used multivitamin, 52% used calcium with vitamin D and 83% used vitamin B₁₂ injections after 5 years. In addition, a decrease in adherence rate from 1 to 5 years after surgery for all supplements except for vitamin B₁₂ was found [7].

Younger patients, patients with major comorbidities, low socioeconomic status, surgical complications, and those with great weight loss, the first year after surgery are more prone to vitamin and mineral deficiency [3, 6]. Several studies have documented that adherence to recommended supplements declines over time after the surgical procedure. Termination due to lack of education may influence, as well as taste and price [6, 8–11].

Objective

This study aims to explore whether patients followed the recommendations on life-long supplementation of vitamins and minerals more than a decade after RYGB surgery and whether patients adhering to supplements had fewer deficiencies compared to patients not following the recommendations.

Methods

Study Design

The Bariatric Surgery Observation Study (BAROBS) is a cross-sectional observation study including all patients who underwent RYGB from 2003 to 2009 in the Central Norway Health Region to a follow-up study from 2018 to 2020. Of 930 invited patients, 546 (59%) participated. Fifty-six patients were excluded from the analyses, presented in the flowchart (Fig. 1). Data from 490 patients on self-reported vitamin and mineral intake and vitamin/mineral status in blood samples have been analyzed. All patients had postoperatively been followed at the outpatient clinic for 2 to 5 years and were invited to participate in an educational program lasting 2 to 3 years [12]. The patients were recommended yearly blood test of ferritin, iron, vitamin D, folate, and vitamin B₁₂. The RYGB procedure in these patients was standardized and performed laparoscopically according to the Lönroth technique; a pouch size of 30–50 ml and with an ante-gastric alimentary limb of 100 cm or 150 cm, depending on BMI below or above 50 kg/m², and a biliopancreatic limb of approximately 50 cm [13].

Postoperative Vitamin and Mineral Recommendations

At time of operation 2003–2009, all patients were recommended life-long supplementation of vitamins and minerals, including an over-the-counter multivitamin-mineral

Fig. 1 The recruitment procedure in the Bariatric Surgery Observation Study (BAROBS) of patients operated by the Roux-en-Y gastric bypass (RYGB) surgical method

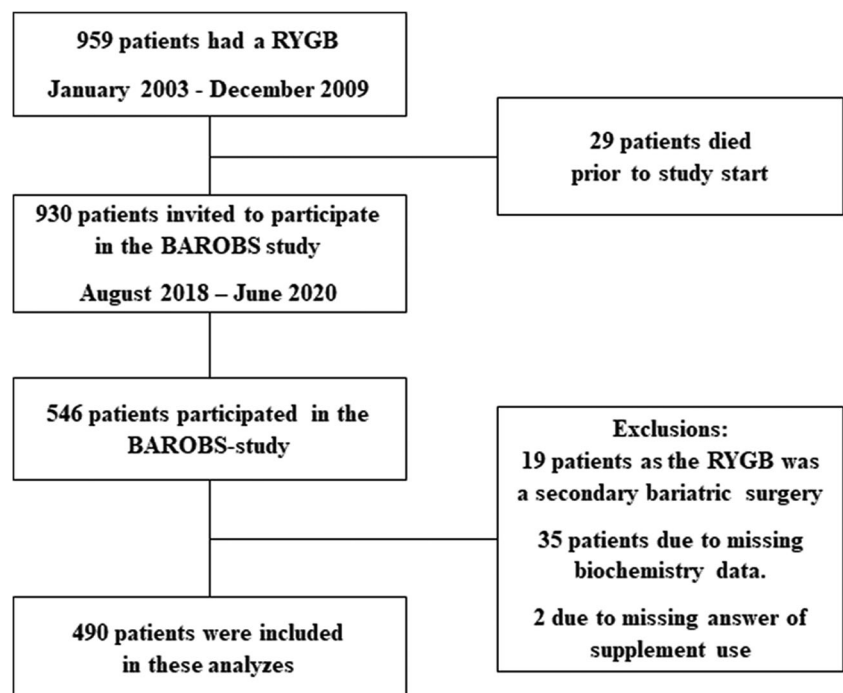


Table 1 Content of vitamins, minerals and trace elements in the most frequently used multivitamin-mineral supplement

Vitamins/minerals/trace elements	Dose
Vitamin A, μg RAE	250
Vitamin B1 (thiamine), mg	1.4
Vitamin B2, (riboflavin) mg	1.6
Vitamin B3 (niacin), mg NE	19
Vitamin B5 (pantothenic acid), mg	5
Vitamin B6 (pyridoxine), mg	1.6
Biotin, μg	30
Folic acid, μg	400
Vitamin B12, μg	2
Vitamin C, mg	75
Vitamin D, μg (IE)	10 (400)
Vitamin E, mg TE	10
Vitamin K1, μg	120
Chrome, μg	35
Iron, mg	15
Iodine, μg	150
Copper, μg	900
Magnesium, mg	100
Manganese, mg	2.3
Molybdenum, μg	45
Selenium, μg	60
Zink, mg	12
Calcium, mg	0

supplement, 1000 mg of calcium carbonate including 20 μg vitamin D, and Vitamin B₁₂ given as an injection of hydroxocobalamin or per oral cyanocobalamin. Only the B₁₂ was covered by reimbursement, which leaves the multivitamin-mineral and the calcium/vitamin D supplement to be paid by the patients. The most frequently used multivitamin-mineral supplement is shown in Table 1. To avoid iron deficiency, per oral iron supplementation was recommended either continuously or intermittently based on ferritin levels at an annual follow-up. Data on iron deficiency have been published in a separate paper [14].

Measurements

Adherence to supplements was self-reported. Fasting venous blood samples were analyzed for thiamine (vitamin B₁), vitamin B₂, vitamin B₆, folate, vitamin B₁₂, vitamin A, vitamin D (measured as the sum of vitamin D₂ (25-OH-kalciferol), and vitamin D₃ (25-OH-kalcidiol)), free calcium, parathyroid hormone (PTH), zinc, copper, methylmalonic acid (MMA), and homocysteine. Samples not analyzed locally were frozen at -20 degrees Celsius and sent to a collaborating laboratory for analysis. This is applied to zinc, copper, vitamin A, vitamin B₁, vitamin B₂, and vitamin B₆. We use the decision

level of 10 nmol/L for folate according to the recommendation from WHO, 75 nmol/L for vitamin D and 350 pmol/L for vitamin B₁₂ and the lower reference value of 186 pmol/L [4, 15–17]. All the laboratories in the study were certified according to ISO:15189. The instruments used for analysis are listed in Supplement 1. PTH is reported as within or above the reference range as the hospitals used different methods and reference values.

Patients are defined to be adherent or non-adherent in three categories: multivitamin-mineral supplements, vitamin B₁₂, and/or calcium with vitamin D.

Statistics

Categorical variables are presented as frequency and percentages and compared using Pearson χ^2 , *p*-values. Normally distributed data are presented as mean \pm SD while non-normally distributed data as the median and interquartile range (Q1–Q3). To compare normally and non-normally distributed data, independent *t*-test and Mann–Whitney were used, respectively. A two-way ANOVA was used to estimate how the mean of quantitative variables changes according to the levels of two categorical variables. Binary logistic regression was performed to find the odds ratio (OR) for nutritional deficiencies in adherent vs non-adherent patients. *p*-values < 0.05 was considered significant. We used IBM SPSS statistics version 29 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 9 (GraphPad Software, LLC, CA, USA).

Results

The 490 patients had a mean \pm SD age at surgery of 40.1 ± 9.0 years and 51.8 ± 9.0 years at follow-up, after 11.7 ± 1.6 years. Three-hundred and ninety-three (80%) were women. Body mass index (BMI) changed from 44.4 ± 5.4 kg/m² to 35.0 ± 7.0 kg/m² (Table 2). A total of 361 (74%) patients reported being adherent to multivitamin-mineral supplements at follow-up, adherence to vitamin B₁₂ was 466 (95%), and calcium with vitamin D was 336 (69%). Among adherent patients, 319/361 (83%) used the same multivitamin-mineral supplement (see Table 1). Per oral vitamin B₁₂ was used in 110/466 (25%) of the adherent patients, while 356/466 (75%) used hydroxocobalamin injections. The recommended calcium with vitamin D (1000 mg/20 μg) was used in 305/336 (91%) adherent patients.

Table 3 presents laboratory test results for the study population 11.7 years after surgery. Vitamin B₂ (Fig. 2b) and vitamin B₆ (Fig. 2c) below lower reference value were present in 103 (29%) and 63 (17%) of patient's adherent, and 67 (52%) and 67 (52%) of patients non-adherent to

Table 2 General characteristics of patient’s (n) adherent (A) or non-adherent (NA) to lifelong multivitamin-mineral supplementation

	n=490	A n=361 (74%)	NA n=129 (26%)	p-value
Sex W/M		295/66	98/31	
Age at baseline (SD) kg/m ²		40.4 (9.0)	39.4 (8.9)	ns
Mean follow-up time (SD) months		140.1 (19.4)	142.1 (18.0)	ns
BMI at baseline (SD) kg/m ²		44.2 (5.3)	44.9 (5.6)	ns
BMI at 10–15 years (SD) kg/m ²		34.5 (6.8)	36.4 (7.3)	0.008
Level of education n (%)		226/347 (65)	92/127 (72)	p=0.134*
< 12 year of school		121/347 (35)	35/127 (28)	
> 12 year of school				
Level of income n (%)		220/346 (64)	93/127 (73)	p=0.049*
< 75,000 Euro		126/346 (36)	34/127 (27)	
> 75,000 Euro				

W women, M=men

SD Standard deviation

*Data analyzed with Pearson Chi-Square

multivitamin-mineral supplements ($p < 0.001$ in both). Thiamine levels indicating deficiency were present in one (less than 1%) adherent and in six (5%) non-adherent patients ($p < 0.001$). Folate (Fig. 2a) was below the decision limit in 39 (11%) adherent and 44 (34%) non-adherent patients ($p < 0.001$). Folate deficiency with simultaneous high homocysteine was present in 37 (8%) patients, seen more often in patients non-adherent 16/129 (12.4%) vs adherent 21/361 (5.8%) ($p = 0.016$).

High vitamin A levels were present in both adherent and non-adherent patients (ns in women, $p = 0.035$ in men). Eight (2%) patients had a vitamin A deficiency, while 25 (5%) had levels above the normal range.

Zinc (Fig. 2e) deficiency was seen in 35 (10%) of the patient’s adherent to multivitamin-mineral supplements and 17 (13%) of the non-adherent patients ($p = 0.25$). A deficiency of copper (Fig. 2f) was not found, but 80 (22%) of the adherent and 39 (30%) non-adherent patients had copper

Table 3 Biochemistry results for patient’s 12 years after Roux-en-Y gastric bypass surgery

Vitamins and minerals (normal range values)	Adherent Median (IQR) n=361	Non-adherent Median (IQR) n=129	p-value	All Median (IQR) n=490	All patients with deficiency n (%)	All patients above upper limit of normal range n (%)
Thiamine (122 nmol/L)	193 (47)	166 (40)	<0.001	186 (47)	7 (1)	
Vitamin B ₂ (264 nmol/L)	292 (73)	261 (66)	<0.001	284 (70)	170 (35)	
Vitamin B ₆ (27 nmol/L)	44 (34)	26 (17)	<0.001	38 (32)	130 (27)	
Folate (> 10 nmol/L*)	24 (20)	11 (10)	<0.001	19 (20)	83 (17)	
Vitamin A (M: 1.1–2.9 μmol/L)	1.9 (0.7)	1.6 (0.6)	0.037	1.8 (0.6)	5 (5)	13 (13)
Vitamin A (W: 1.2–2.4 μmol/L)	1.8 (0.6)	1.7 (0.5)	0.098	1.8 (0.6)	9 (2)	20 (5)
Zinc (11.2–19.0 μmol/L)	12.9 (2.0)	13.0 (1.7)	0.250	13.0 (1.9)	52 (11)	1 (<1)
Copper (10.7–22.0 μmol/L)	19.2 (4.2)	20.0 (4.8)	0.024	19.5 (4.2)	0	119 (24)
Vitamin B ₁₂ ♦ (> 350 pmol/L*)	635 (704)	278 (89)	<0.001	611 (697)	94 (19)	
Vitamin B ₁₂ ♦ (> 186 pmol/L)					7/490 (1)	
Vitamin D ♣ (> 75 nmol/L*)	73 (33)	52 (34)	<0.001	68 (38)	294 (60)	
Free calcium ♣ (1.18–1.32 mmol/L)	1.18 (0.05)	1.18 (0.03)	0.836	1.18 (0.05)	190 (39)	4 (<1)

Data are presented as median (IQR) and frequencies (percentages) of adherent, non-adherent and all patients

*For the vitamin’s folate, vitamin B₁₂, and vitamin D, the decision limits are presented instead of reference normal range values

♦Number of patients adherent to vitamin B₁₂ 466/490

♣Number of patients adherent to calcium with vitamin D 336/490

M Men, n=97; W Women, n=393

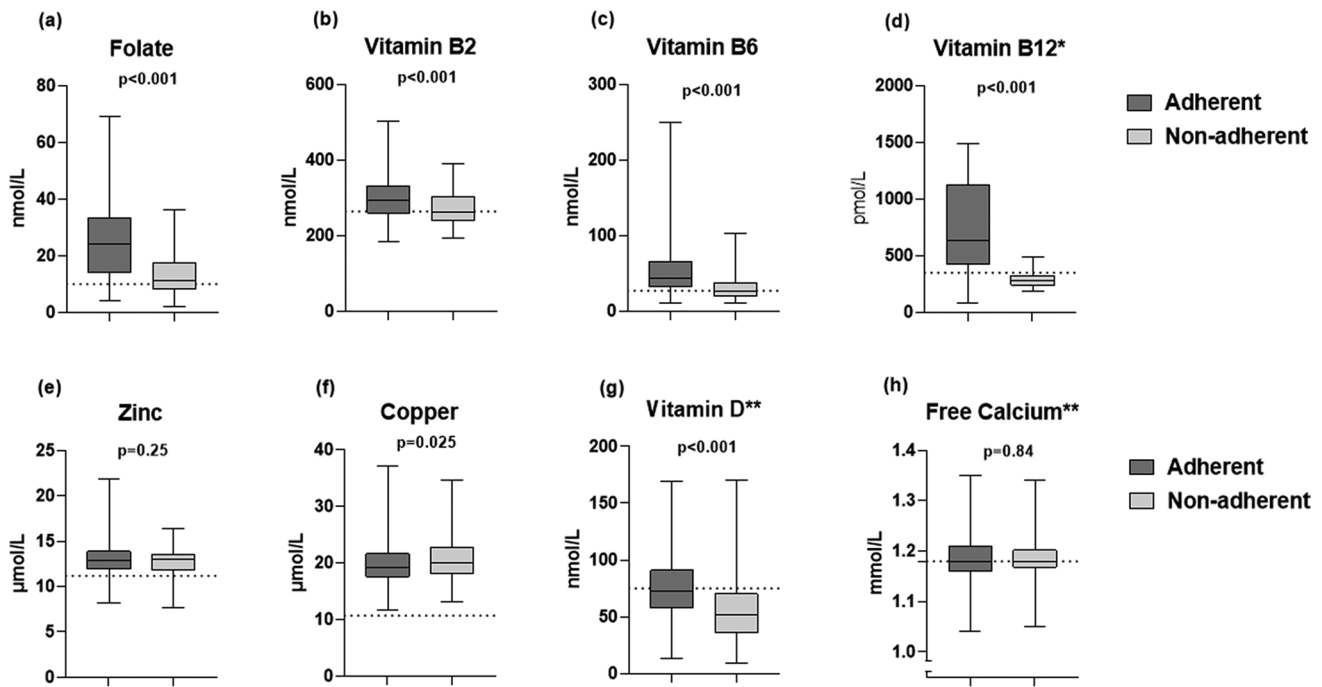


Fig. 2 Median (min, max) serum concentrations of folate (a), vitamin B₂ (b), vitamin B₆ (c), zinc (e), and copper (f) in patients adherent or non-adherent to multivitamin-mineral supplements. *Median (min, max) serum concentrations of vitamin B₁₂ (d) in patients adher-

ent or non-adherent to vitamin B₁₂ supplements **Median (min, max) serum concentrations of vitamin D (g) and free calcium (h) in patients adherent or non-adherent to calcium with vitamin D supplements. Lower reference values are marked with a dotted line

levels above upper reference levels ($p=0.025$). Among those with high copper levels, six patients had elevated ceruloplasmin levels.

Although adherence to vitamin B₁₂ (Fig. 2d) was as high as 466 (95%), sub-optimal levels were seen in 73 (16%) patients, compared to 21 (75%) patients in the non-adherent group ($p < 0.001$). Seven patients had below 186 pmol/L, which was present in both adherent/non-adherent patients.

Adherence to calcium/vitamin D supplements (1000 mg/20 µg) was reported by 336 (69%) patients (Fig. 2g). Sub-optimal level (< 75 nmol/l) of 25-hydroxy vitamin D was seen in 174/336 (52%) adherent patients, compared to 120/154 (78%) non-adherent patients ($p < 0.001$). Parathyroid hormone (PTH) (Table 4) was

above the reference level in 196 (40%) patients. Among all patients, 190 (39%) had levels below the normal range for free calcium (Fig. 2h), while four patients ($< 1\%$) had values above ($p=0.84$).

The OR of having blood values in the normal or optimal range were 2.7, 5.2, 4.3, and 3.3 times higher in adherent patients vs non-adherent patients for vitamin B₂, vitamin B₆, folate, and vitamin D, respectively, all p -values < 0.001 .

Discussion

The main finding in our study was that three out of four patients followed these recommendations of life-long multi-vitamin-mineral supplements 12 years after RYGB. Nearly

Table 4 Frequency and prevalence of patient’s adherent (A-Ca) or non-adherent (NA-Ca) to Calcium supplement with vitamin D and normal or elevated PTH at different levels of Vitamin D

Vitamin D	A-Ca	NA-Ca	Pearson χ^2	Normal PTH	Elevated PTH	Pearson χ^2
25-OH D < 50 nmol/L	50 (10%)	73 (15%)		53 (11%)	70 (14%)	
25-OH D > 50 nmol/L	286 (58%)	81 (17%)	$P < 0.001$	241 (49%)	126 (26%)	$P < 0.001$
25-OH D < 75 nmol/L	174 (36%)	120 (25%)		143 (29%)	151 (31%)	
25-OH D > 75 nmol/L	162 (33%)	34 (7%)	$P < 0.001$	151 (31%)	45 (9%)	$P < 0.001$
25-OH D < 100 nmol/L	278 (57%)	146 (30%)		247 (50%)	177 (36%)	
25-OH D > 100 nmol/L	58 (12%)	8 (2%)	$P < 0.001$	47 (10%)	19 (4%)	$P = 0.03$

all patients used recommended vitamin B₁₂, and seven out of ten used calcium with vitamin D. The patients used over-the-counter supplements, as specialized multivitamin-mineral supplements for RYGB patients were unavailable until 2017 in Norway. Some patients experience side effects from supplements [11], which might contribute to the lower adherence rate of the chewing calcium supplement in this study. Still, compared to studies from other countries, adherence to recommended supplements in the present study was high [8–10].

Serum folate level has been suggested to indicate adherence to multivitamin-mineral supplementation [6]. Ten percent of the adherent patients and more than 30% of the non-adherent patients were below the decision limit of folate. At the same time, vitamin B₂ and vitamin B₆ deficiency were more common in both adherent (30% and almost 20%, respectively) or/and non-adherent (in more than 50%) patients. Another ten-year follow-up study of 431 with RYGB found lower prevalence of folate deficiency (< 8 nmol/L) with 12% of the total patient population while 24% used a multivitamin and 20% used a folate supplement [10]. If folate is low, the patients may be deficient in several B vitamins and the recommendation of multivitamin supplements is reasonable. Some countries fortify food with synthetic folate (folic acid), which is not the case in Norway.

Zinc and copper are absorbed predominantly in the duodenum and jejunum, competing with iron [18]. We found no correlation between zinc and copper and no difference between adherent or non-adherent patients regarding zinc deficiency. Reports on long-term results of copper are scarce, but a two-year follow-up study found 9.6% of the patients to be deficient in copper [19]. We did not find copper deficiency, but one in four had high values of copper. Only six of these also had elevated ceruloplasmin, and the high copper values are probably due to medical conditions. This is not in accordance with a recent pre- and one-year postoperative study, which found a median below the reference level [20].

A deficiency of vitamin B₁₂ can result in neurologic complications such as peripheral neuropathy, ataxia, cognitive impairment, depression, and fatigue in mild or extreme forms [21]. One in four patients in BAROBS used per-oral vitamin B₁₂ supplements, while the rest of the adherent patients used hydroxocobalamin intramuscular injections every second or third month. The American Society for Metabolic and Bariatric Surgery (ASMBS) Guidelines 2019 recommends orally 350–1000 µg/day or 1000 µg/month intramuscularly or subcutaneously [5]. Vitamin B₁₂ is measured as circulating total B₁₂, which leaves the biologically active vitamin B₁₂ level unknown. Clinically, methylmalonic acid (MMA) and homocysteine are only measured when vitamin B₁₂ and folate deficiency are suspected. Almost one in five patients in the present study had elevated MMA, indicating that the supplementation of vitamin B₁₂ is too low.

It has been suggested that giving vitamin B₁₂ injections at patients' request is harmless, as there is no defined tolerable upper level [22, 23]. The high adherence rate to vitamin B₁₂ supplements in the BAROBS study is similar to findings in a five-year study from Norway [7]. Public hospitals and national reimbursement of vitamin B₁₂ supplements may contribute to the high adherence rate as well as the symptoms of vitamin B₁₂ deficiency are more recognizable for the patients with lack of energy, irritability, and emotional lability. Only seven patients (1.4%), both adherent and non-adherent, had vitamin B₁₂ below 186 pmol/L.

Most patients were adherent to recommended calcium with vitamin D supplements, and the multivitamin-mineral supplement also contained vitamin D. Nevertheless, only 40% of the patients had vitamin D above 75 nmol/L, and 40% had free calcium below the reference value. Vitamin D enhances calcium and phosphorus absorption, and low levels may have contributed to low BMD. Ten years after surgery, the most significant fall (25%) in BMD occurred within the first 5 years after surgery [24]. The elevated PTH occurrence in the BAROBS study is comparable to another study with a seven-year follow-up of 70 patients with RYGB and 72 patients with a sleeve gastrectomy [25]. Nine percent (45/490) of the patients in the BAROBS study had elevated PTH levels even when vitamin D was above 75 nmol/L. Recent studies have shown that a vitamin D level above 75 nmol/L is needed to have a PTH in the normal range after RYGB [24, 26, 27]. The BAROBS study supports these findings and even adherent patients need more vitamin D. The BOMSS Guidelines 2020 recommends a higher and more specific dose of vitamin D compared to the Guidelines of 2016; the new range is 50–100 µg/day (2000–4000 IU) until 75 nmol/L is reached [4] [28]. Patients' adherent are more than three times more likely to have an optimal (> 75 nmol/L) vitamin D level than non-adherent patients.

The main strengths of the BAROBS study are a long-term follow-up (mean 11.7 years), the high number of comparable surgical patients (*n* = 490) and data reflecting a real-time follow-up of patients after obesity surgery. The recommendations for supplements and the follow-up program have been similar in the region. However, the self-reported use of supplements might be overestimated. At time of surgery in 2003–2009 and during the two-to-five-year postoperative follow-up, the patients were recommended an over-the-counter multivitamin-mineral supplement, calcium/vitamin D (1000 mg/20 µg) and vitamin B₁₂ injections. Only vitamin B₁₂ was reimbursed. Bariatric supplements became available in Norway in 2017 but were more expensive and not easily accessible. It is also considered a limitation that we do not know the daily/weekly number of multivitamin-mineral or calcium/vitamin D tablets the patients took. We assume that most patients followed the recommendations given at the time of surgery; however, some patients may have increased

their supplements according to updated guidelines after advice from health professionals, or on their own initiative.

Laboratory tests on vitamins have some limitations on individual levels as the values are snapshots of the patient's status, and the water-soluble vitamins fluctuate with intake [29]. However, this is not considered a limitation with the high number of patients in the BAROBS study. The BAROBS study may underestimate the general deficiency rate in a post-RYGB population. We may assume that patients (384/930) lost to follow-up may be less adherent to the lifestyle changes and multivitamin-mineral use than patients participating.

Continuous improvement in patient education programs either in-person or digitally with a multidisciplinary team, emphasizing life-long supplementation, the first few years after surgery empowers the patient's ability to take healthy choices. Updated information on follow-up after obesity surgery should be easily available to general practitioners responsible for the long-term care for these patients. The advice regarding supplements must be easy to follow and the supplements affordable.

Conclusion

Adherence to supplements, though in sub-optimal doses of new recommendations, decrease the probability of vitamin and mineral deficiency, especially for thiamine, vitamin B₂, vitamin B₆, folate, vitamin B₁₂, and vitamin D, but does not eliminate it. Twelve years after RYGB, most patients follow the recommendations of daily multivitamin-mineral, vitamin B₁₂, and calcium with vitamin D. These results may be relevant for medical practitioners and multidisciplinary teams treating patients with obesity and after bariatric surgery.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11695-023-06787-w>.

Acknowledgements We want to thank all participants for their time and commitment, and the staff at the obesity outpatient clinics at Namsos Hospital, the Center for Obesity at St. Olav's Hospital, Trondheim University Hospital, and the Clinical Research Unit, Møre & Romsdal Hospital trust, Ålesund for their invaluable effort in data collection.

Author Contribution Conceptualization: K.K.B., J.S., S.N., S.S., and D.A.L.H.; methodology: K.K.B., J.S., and D.A.L.H.; formal analysis: K.K.B. and S.S.; investigation: K.K.B., J.S., S.N., G.J., B.E.K., Å.A.H., H.G., and D.A.L.H.; data curation: J.S.; writing—original draft preparation: K.K.B.; writing—review and editing all authors; supervision: J.S., K.L.H., and D.A.L.H.; project administration: J.S.; funding acquisition: J.S.; and D.A.L.H. All authors have read and agreed to the published version of the manuscript.

Funding Open access funding provided by Volda University College The Liaison Committee for Education, Research and Innovation in Central Norway and Norwegian University of Science and Technology

(NTNU) Norway, grant number 46055500. Funding from all three local hospital trusts, St. Olav's Hospital, Trondheim University Hospital, Norway, Møre & Romsdal Hospital Trust, Norway (Grant number P-101618–01) and Nord-Trøndelag Hospital Trust, Norway.

Data Availability The raw data supporting the conclusions of this article will be made available by the authors on request.

Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The BAROBS was approved by The Regional Committee for Medical Research Ethics South East Norway (REK 2017/1828–21). All participants provided written informed consent before enrollment in the study.

Conflict of Interest The authors declare no competing interests.

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