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ORIGINAL CONTRIBUTIONS

Do Specialized Bariatric Multivitamins Lower Deficiencies After Sleeve Gastrectomy?

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Abstract

Background Vitamin and mineral deficiencies are common after a sleeve gastrectomy (SG). The aim of this study is to examine the effectiveness of a specialized bariatric multivitamin (WLS Optimum) for SG patients on deficiencies compared with a regular multivitamin (MVS) for up to 5 years.

Methods Data of all patients who underwent a SG procedure in the Catharina Hospital Eindhoven (CZE) between July 2011 and July 2016 were collected and retrospectively analyzed. All patients who completed a preoperative blood test and at least one blood withdrawal during the first operative year were included in this study.

Results This study included 970 patients; 291 patients in the WLS-user group and 679 patients in the non-WLS-user group. In favor of the user group, significantly less de novo deficiencies were found of vitamin B_1 (2 years) and vitamin B_6 (two and three), folic acid (1 and 2 years), and vitamin B_{12} (at 1 year). Binomial logistic regression showed a significant influence of multivitamin supplementation mainly on ferritin; vitamins B_1, B_6, B_{12}, and D; and folic acid, (all $p < 0.05$). The total number of de novo deficiencies was significantly reduced during the whole study for all WLS Optimum users.

Conclusions Vitamin deficiencies are common, and postoperative nutritional management after SG is underestimated. The use of a specialized multivitamin supplement resulted in higher mean serum concentrations and less deficiencies of vitamin B_1, folic acid, and vitamin B_{12}. This study shows that SG patients benefit from the specialized multivitamin supplements, but adjustments are required for iron and vitamin B_6 content.

Keywords Obesity · Bariatric surgery · Sleeve gastrectomy · Vitamin · Mineral · Deficiency · Specialized · Multivitamin · Supplementation

Introduction

The World Health Organization has declared obesity as one of the most serious public health issues. A raised BMI increases the risk of comorbid conditions such as cardiovascular diseases, which were the leading cause of death in 2012; diabetes mellitus; musculoskeletal disorders; and some types of cancers. In 2016, almost two billion adults, 18 years and older,

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were deemed overweight. Of these, over 650 million were obese [1]. Bariatric surgery (BS) is recognized as a highly effective therapy for obesity because of the significant weight loss, reduction of obesity-related comorbidities, and improvement in the quality of life [2–4]. Long-term results have shown that the Roux-en-Y gastric bypass (RYGB) can be regarded as the gold standard, but nowadays, the sleeve gastrectomy (SG) is the most performed alternative [4]. The majority of the stomach's capacity is resected with this technique without any additional small-bowel reconstruction. Early results of the SG show the safety and effectiveness of this procedure in terms of complications, weight loss, and remission of comorbidities [3, 5–9].

In spite of multiple clinical benefits, vitamin and mineral deficiencies are quite common after bariatric surgery. These deficiencies develop postoperatively as a consequence of reduced intake; food intolerance; changes in taste and eating patterns; malabsorption of nutrients, vitamins, and minerals; and non-adherence to dietary and supplementation recommendations. Besides these, a high prevalence of deficient nutrient status prior to bariatric surgery is reported in many studies [10–15].

After bariatric surgery, these micronutrient deficiencies increase or occur de novo, and may result in serious complications when left unattended [5, 16, 17]. Preventing vitamin and mineral deficiencies after BS is hard to achieve with standard multivitamin supplements (MVS), especially when deficits are present before BS. Standard supplements showed to be ineffective to prevent new and restore preoperative deficiencies on the long term [18–20]. Therefore, customized MVS for post-BS patients were developed, named weight loss surgery (WLS) Optimum and WLS Forte, for SG and RYGB, respectively.

The randomized controlled trial (RCT) of Dogan et al. [21] compared the difference in deficiencies between WLS Forte users and regular MVS users after RYGB. This RCT was continued by a cohort study of Homan et al. [22] with a follow-up of 3 years. These studies already reported on the efficacy of this WLS Forte supplement in a completely controlled setting with multivitamins provided free of charge and concluded that the use of this supplement for 1 year resulted in significantly less deficiencies of ferritin, vitamin B_{12}, and folic acid compared with regular MVS. However, this analysis has not yet been performed for the SG patients. A lot of deficiencies were frequently found after SG, especially deficiencies in iron (29–64%), folic acid (13–18%), vitamin B_{12} (14–20.0%), and vitamin D (67–89%), and an elevated parathyroid hormone (PTH) (15–60%) was frequently found after SG. Some of these deficits are reasons to develop for example anemia (20%) [5, 18]. To prevent these vitamin and mineral deficiencies after GS, lifelong supplementation is recommended, but long-term data on deficiencies are still lacking [18–20].

The aim of this study is to examine the effectiveness of the WLS Optimum in a normal clinical setting for SG patients on deficiencies compared with a regular MVS for up to 5 years. We hypothesize that specialized WLS supplements lead to less vitamin and mineral deficiencies compared with regular MVS.

Methods

Study Design and Patients

In this single-center study, data of all patients who underwent a SG procedure in the Catharina Hospital Eindhoven (CZE) between July 2011 and July 2016 were collected and retrospectively analyzed. All patients who completed a preoperative blood test and at least the 6-month withdrawal were included in this study. To ensure a more homogenous group, exclusion criteria were conditions which could cause serious metabolic changes: cancer, hemochromatosis, or high serum ferritin concentrations in combination with elevated serum-reactive protein, creatinine levels > 150 mmol/L, or liver enzymes greater than two times of the reference value.

The study protocol was approved by the National Medical Ethics Review Committee of the Radboud University Medical Center (protocol number 2017-3412) and Local Ethical Committee of the CZE (protocol number nWMO2017-45), and was conducted in concordance with the principles of the Declaration of Helsinki.

Postoperatively, all patients received pantoprazole (40 mg/day) for 3 months and fraxiparin (5000 units/day) for 4 weeks. All patients start with CalcichewD$_3$ (1000 mg calcium carbonate/800 IU colecalciferol) and a MVS: WLS Optimum supplement. When patients were unwilling to use WLS Optimum a regular MVS in concentrations of 100% of the recommended daily intake (RDI) was advised. Table 1 gives an overview of the compositions. Additional to these supplements, we started prescribing 50,000 international units of liquid colecalciferol once a month since 2016.

All patients followed a strict postoperative 5-year follow-up program consisting of four visits to the outpatient clinic during the first postoperative year (at 6 weeks, 3 months, 6 months, and 1 year) and twice a year for the next 4 years. Two groups were compared in this analysis, the users (WLS Optimum) and the non-users.

Surgical Procedure

All patients underwent the laparoscopic SG following a standardized operating technique, performed by six dedicated bariatric surgeons. The general inclusion criteria for bariatric surgery were applicable [3, 19]. The gastrocolic ligament and gastroepiploic vessels were freed from the greater curvature of the stomach, using the Ligasure™ (Medtronic ValleylabTM, Boulder, Colorado, USA). A 34 French

Table 1 Composition of regular MVS and WLS Optimum

		Regular MVS		WLS Optimum	
Ingredients	Value	Dosage	RDA (%)	Dosage	RDA (%)
Calcium	mg	160	20	–	–
Chloride	mg	–	–	–	–
Chrome	μg	25	63	40	100
Copper	mg	1.5	150	1	100
Folic acid	μg	200	100	300	150
Iodine	μg	150	100	150	100
Iron	mg	14	100	21	150
Manganese	mg	2.5	125	3	150
Magnesium	mg	125	33	30	8
Molybdeen	μg	25	50	50	100
Phosphorus	mg	105	15	–	–
Selenium	μg	25	45	55	100
Vitamin A	μg	800	100	1000	125
Vitamin B_1	mg	1.1	100	2	182
Vitamin B_2	mg	1.4	100	2	143
Vitamin B_3	mg	16	100	25	156
Vitamin B_5	mg	6	100	9	150
Vitamin B_6	mg	1.4	100	2	143
Vitamin B_8	μg	50	100	150	300
Vitamin B_{12}	μg	2.5	100	10	400
Vitamin C	mg	80	100	100	125
Vitamin D	μg	5	100	7.5	150
Vitamin E	mg	12	100	12	100
Vitamin K	μg	75	100	90	120
Zinc	mg	15	150	15	150

MVS, multivitamin supplementation; *RDA*, recommended daily allowance; *WLS*, weight loss surgery; *mg*, milligram; *μg*, microgram

orogastric tube was introduced along the lesser curvature up to the pylorus. Transection of the stomach was performed using the EndoGIA™, with Tri-Staple™ cartridges, progressing upwards from 4 to 6 cm orally from the pylorus. The first staple was placed transversely, and for subsequent staplers, the staple line was aimed towards the angle of His, taking care not to narrow the incisura. The excised gastric specimen was removed through the somewhat enlarged left trocar site.

Laboratory Analysis and Treatment of Deficiencies

Standard laboratory evaluation, consisting of a complete blood count, mean cell volume (MCV), and vitamin and mineral status, was performed for preoperative assessment, at 6 and 12 months after surgery and annually until the fifth postoperative year. Deficiencies that were found either preoperatively or postoperatively were supplemented. Treatment regimens and laboratory reference values are described in Table 2.

Biochemical Assay

The utilized laboratory for our study is certified by the Dutch Association of Clinical Chemistry Labs (CCKL, registration number R0125). Independent clinical chemists did the biochemical analysis of the vitamins and minerals. Vitamin A was determined as retinol in serum with an UPLC-TUV (Waters®) instrument using Recipe® reagents. Vitamin B_1 (thiamin pyrophosphate) and vitamin B_6 (pyridoxal-5-phosphate) were determined in EDTA-whole blood with Chromsystems® reagents on a UPLC–FLR (Waters®) device. Vitamin D (25-hydroxy vitamin D) was determined in serum by an immunometric competition assay on Liason® using Diasorin® reagents. Vitamin B_{12} (cobalamin) serum, folate serum and ferritin heparin plasma were analyzed by immunometric assays on the cobas E-module Roche®. Magnesium was determined in heparin plasma by a colorimetric endpoint assay on the cobas C-module Roche®. Zinc was determined in plasma on an atomic absorption spectrometer (PerkinElmer®).

Data Collection and Statistical Analysis

Anonymized data on multivitamin usage were available in the Catharina Hospital. This is part of a standard procedure during follow-up. These data were matched with the Catharina Hospital laboratory database made for this analysis using date of birth and date of operation (by author SvL). After matching, dates of birth and operation dates were removed.

All data were analyzed using IBM SPSS Statistics version 22 for Windows (IBM Corp., Armonk, NY, USA). Data are expressed as mean (± standard deviation), unless otherwise specified.

Differences between groups were calculated using Student's t test for continuous data and chi-square tests for ordinal/nominal data (or Fisher's exact test was used when counts were < 5). Independent samples t test for mean serum levels and binary logistic regression for repeated-measures design were used to analyze the effect of MVS on serum concentrations. Gender and age groups ≤ 35 years, 36–59 years, and ≥ 60 years were included in the model as confounders. Once a deficiency occurred in a patient, this patient was considered deficient for the rest of the follow-up of the study for that specific deficiency only. A p value < 0.05 was considered statistically significant.

Results

This study included 970 patients; 291 patients in the WLS-user group and 679 patients in the non-WLS-user group. As expected, many patients were lost during follow-up in both

Table 2 Normal serum levels and supplementation schemes

Serum variables	Normal range	Treatment of deficiency
Hemoglobin (mmol/L)	Male > 8.5 Female > 7.5	200 mg Ferro Fumarate + 500 mg ascorbic acid daily for 3 months
Hematocrit (L/L)	0.40–0.50	NA
MCV (fL)	80–100	NA
Iron (μmol/L)	Male > 14.0 Female > 10.0	Treatment depends on ferritin
Ferritin (μg/L)	> 20	200 mg Ferro Fumarate + 500 mg ascorbic acid daily for 3 months
Folate (nmol/L)	> 10.0	0.5 mg folic acid daily for 3 months
Vitamin B_1 (nmol/L)	> 90.0	50 mg thiamin daily for 3 months
Vitamin B_6 (nmol/L)	35.1–110.0	NA
Vitamin B_{12} (pmol/L)	≥ 200.0	Intramuscular hydroxocobalamin injections with 1000 μg of cobalamin, once per 2 weeks in the first 2 months and once per 3 months afterwards
Vitamin D (nmol/L)	> 50	50,000 IU colecalciferol weekly during the first 6 weeks, monthly afterwards
PTH (pmol/L)	1.6–6.9	NA
Calcium (mmol/L)	2.10–2.55	NA
Albumin (g/L)	35–55	NA
MMA (nmol/L)	< 300	NA

MCV, mean cell volume; *PTH*, parathyroid hormone; *MMA*, methyl malonic acid; *NA*, not applicable

groups (Table 2). Baseline characteristics of all included patients are described in Table 3. Preoperatively, 70 vs 76% of patients had one or more deficiencies respectively in the user and non-user groups ($p = 0.021$).

Table 3 shows the baseline characteristics of the user and non-user groups. There was a significant difference in the prevalence in type 2 diabetes, with a higher percentage in the user group (22.0 vs 17% $p = 0.045$). Also, more patients suffered from gastroesophageal reflux disease in the user group (22 vs 17%, p 0.045). In terms of preoperative deficiencies, there was a significantly higher number of folic acid–deficient patients in the non-user group ($p = 0.024$), but a lower rate in hypervitaminosis for vitamin B_6 ($p = 0.042$).

Table 4 gives an overview of the mean serum concentrations at 6 months, 1–4 years postoperatively for users and non-users. Significant differences were found in delta serum levels in favor of the user group for folic acid (6 months and 2 years), vitamin B_1 (6 months, 1 and 3 years); vitamin B_{12} (6 months and 1 year); and vitamin D (6 months and 1 year). Anemia was less prevalent in the standard multivitamin group and delta calcium lower after 2 years.

Table 5 shows the percentages of preoperative deficiencies in the user and non-user groups, and de novo deficiencies in the postoperative period. In favor of the user group, significantly less de novo deficiencies were found for folic acid (1 and 2 years), vitamin B_1 (year 2), and vitamin B_{12} (year 1). Hypervitaminosis for vitamin B_6 was significantly more prominent in users at 1 and 2 years. On the contrary, at 2 and 3 years, there were significantly higher percentages of de novo anemia cases. The total

Table 3 Baseline characteristics (mean ± SD or *N* (%))

	Non-user group	User group	*P* value
Age (years)	43 ± 11	46 ± 10	*0.001*
Weight (kg)	127 ± 22	125 ± 18	0.13
BMI (kg/m^2)	44 ± 6	43 ± 5	*0.011*
Male/female (*N*, %)	154 (25%)/475 (75%)	112 (33%)/229 (67%)	*0.005*
Comorbidities (*N*, %)			
DM type II	105 (17%)	75 (22%)	*0.045*
Hypertension	232 (37%)	134 (40%)	0.49
Dyslipidemia	115 (19%)	57 (20%)	0.60
GERD	104 (17%)	73 (21%)	*0.045*
OSAS	101 (16%)	68 (20%)	0.13

BMI, body mass index; *DM*, diabetes mellitus; *MVS*, multivitamin supplementation; *GERD*, gastroesophageal reflux disease; *OSAS*, obstructive sleep apnea syndrome

Table 4 Mean serum concentrations (± SD) and deltas for users and non-users. Baseline: users *N* = 291, non-users *N* = 679

Serum variables	Months of FU	*N* users	Users (mean ± SD)	*N* non-users	Non-users (mean ± SD)	*P* value	Users Δ from baseline ± SD	Non-users Δ from baseline ± SD	*P* value
Hb	6	283	8.6 ± 0.7	664	8.6 ± 0.7	0.62	− 0.25 ± 0.51	− 0.18 ± 0.53	0.041
	12	223	8.5 ± 0.7	594	8.5 ± 0.7	0.52	− 0.32 ± 0.60	− 0.27 ± 0.55	0.044
	24	201	8.5 ± 0.7	616	8.5 ± 0.7	0.63	− 0.31 ± 1.04	− 0.01 ± 0.94	0.001
	36	120	8.3 ± 0.9	137	8.5 ± 0.8	0.06	− 0.44 ± 1.05	0.00 ± 0.91	< 0.001
	48	80	8.3 ± 0.9	53	8.5 ± 0.8	0.09	− 0.30 ± 1.05	− 0.07 ± 0.99	0.048
MCV	6	283	88.4 ± 4.2	664	89.0 ± 4.4	0.12	1.4 ± 2.9	1.4 ± 2.9	0.82
	12	223	89.2 ± 4.0	594	89.6 ± 4.4	0.16	2.2 ± 3.0	2.1 ± 2.8	0.62
	24	201	89.2 ± 4.0	616	89.6 ± 4.4	0.22	2.9 ± 6.5	1.3 ± 6.1	*0.004*
	36	120	89.4 ± 5.5	137	88.8 ± 4.3	0.30	2.8 ± 6.4	1.0 ± 6.8	*0.033*
	48	80	89.0 ± 5.7	53	87.9 ± 4.6	0.28	2.4 ± 6.7	1.7 ± 6.8	0.54
Iron	6	284	15.6 ± 5.4	665	15.6 ± 5.7	0.32	3.2 ± 5.2	2.8 ± 5.6	*0.041*
	12	223	15.8 ± 5.2	594	16.2 ± 5.9	0.32	3.6 ± 5.8	3.4 ± 5.9	0.30
	24	201	16.0 ± 5.2	616	16.1 ± 5.9	0.72	4.9 ± 7.8	45.3 ± 7.5	0.57
	36	120	16.6 ± 7.4	137	16.7 ± 6.2	0.93	4.4 ± 8.5	4.3 ± 7.7	0.99
	48	80	16.3 ± 6.0	53	16.6 ± 6.4	0.73	4.2 ± 7.3	5.5 ± 7.8	0.33
Ferritin	6	284	152.9 ± 109.0	665	136.1 ± 110.0	0.031	2.0 ± 81.6	3.1 ± 74.4	0.83
	12	223	143.1 ± 115.2	594	128.7 ± 110.6	0.10	− 3.7 ± 81.2	− 5.8 ± 79.7	0.78
	24	202	125.5 ± 146.3	275	115.2 ± 108.6	0.38	− 12.1 ± 143.5	6.7 ± 113.2	0.11
	36	120	107.9 ± 105.7	137	102.6 ± 106.6	0.69	− 15.5 ± 143.3	− 8.7 ± 108.2	0.67
	48	80	96.4 ± 117.0	53	97.0 ± 96.1	0.97	− 11.5 ± 148.6	− 13.9 ± 103.7	0.28
PTH	6	284	5.1 ± 1.9	665	5.3 ± 2.2	0.31	− 2.1 ± 2.9	− 1.8 ± 2.4	0.12
	12	223	5.5 ± 1.9	594	5.5 ± 2.2	0.74	− 1.7 ± 2.8	− 1.6 ± 2.6	0.09
	24	201	5.4 ± 1.8	616	5.6 ± 2.2	0.46	− 1.3 ± 4.4	− 1.5 ± 3.7	0.57
	36	120	5.9 ± 2.6	137	6.3 ± 2.4	0.17	− 1.1 ± 4.3	− 0.6 ± 3.6	0.30
	48	80	5.9 ± 2.2	53	6.5 ± 2.6	0.21	− 0.8 ± 4.1	− 0.4 ± 3.5	0.58
Calcium	6	284	2.39 ± 0.09	665	2.38 ± 0.09	0.10	0.01 ± 0.09	0.01 ± 0.09	0.77
	12	223	2.37 ± 0.09	594	2.35 ± 0.09	0.12	− 0.01 ± 0.09	− 0.01 ± 0.09	0.78
	24	201	2.37 ± 0.09	616	2.36 ± 0.09	0.051	− 0.04 ± 0.13	− 0.01 ± 0.13	*0.004*
	36	120	2.34 ± 0.08	137	2.34 ± 0.09	0.58	− 0.05 ± 0.11	− 0.02 ± 0.13	0.16
	48	80	2.33 ± 0.09	53	2.36 ± 0.08	0.11	− 0.05 ± 0.12	− 0.02 ± 0.12	0.15
Albumin	6	284	44.0 ± 2.5	665	43.4 ± 2.5	*0.039*	− 1.4 ± 2.3	− 1.2 ± 2.4	0.36
	12	223	43.9 ± 2.5	594	43.6 ± 2.6	0.08	− 1.1 ± 2.5	− 1.0 ± 2.5	0.33
	24	201	44.1 ± 2.5	616	43.7 ± 2.6	*0.025*	− 1.0 ± 3.8	− 0.7 ± 3.4	0.24
	36	120	43.6 ± 2.6	137	43.4 ± 2.3	0.64	− 1.5 ± 3.8	− 1.0 ± 3.0	0.33
	48	80	43.3 ± 2.5	53	43.7 ± 2.4	0.32	− 1.4 ± 3.3	− 0.8 ± 3.5	0.36
Vitamin D	6	284	88.0 ± 23.3	665	80.0 ± 24.0	*< 0.001*	46.2 ± 25.2	40.6 ± 25.2	*0.002*
	12	223	82.8 ± 23.4	594	75.2 ± 24.8	*< 0.001*	45.9 ± 25.2	40.8 ± 25.3	*0.005*
	24	202	63.4 ± 20.9	275	66.0 ± 21.5	0.19	22.6 ± 29.3	27.4 ± 28.2	0.07
	36	120	62.5 ± 19.0	135	65.6 ± 23.3	0.25	22.3 ± 27.2	25.7 ± 28.0	0.34
	48	80	65.7 ± 21.1	52	67.3 ± 21.8	0.69	23.5 ± 30.4	24.7 ± 27.9	0.82
Vitamin B_1	6	284	143.6 ± 28.1	665	137.0 ± 45.5	*0.025*	4.6 ± 33.8	− 4.4 ± 59.0	*0.017*
	12	223	150.8 ± 30.0	594	140.2 ± 47.3	*0.001*	4.6 ± 33.7	− 4.3 ± 58.9	*0.019*
	24	201	141.5 ± 28.3	275	139.8 ± 34.5	0.56	0.9 ± 41.7	3.6 ± 47.3	0.52
	36	119	140.3 ± 32.7	197	145.6 ± 29.8	0.18	0.6 ± 38.4	11.0 ± 43.3	*0.046*
	48	79	159.0 ± 100.8	52	150.2 ± 33.3	0.54	12.5 ± 40.2	14.7 ± 37.6	0.75
Vitamin B_6	6	284	111.2 ± 64.6	665	110.4 ± 85.8	0.89	18.4 ± 133.0	28.1 ± 94.3	0.20
	12	221	119.5 ± 92.1	591	107.4 ± 66.2	0.13	18.1 ± 134.0	28.2 ± 94.1	0.19
	24	201	113.8 ± 54.7	275	101.7 ± 73.6	*0.040*	18.8 ± 135.9	21.2 ± 110.2	0.83

Table 4 (continued)

Serum variables	Months of FU	*N* users	Users (mean ± SD)	*N* non-users	Non-users (mean ± SD)	*P* value	Users Δ from baseline ± SD	Non-users Δ from baseline ± SD	*P* value
	36	119	118.1 ± 81.6	134	98.6 ± 37.2	*0.014*	30.0 ± 129.3	22.4 ± 79.7	0.57
	48	79	98.0 ± 48.8	52	101.1 ± 39.9	0.70	8.0 ± 126.9	23.0 ± 52.9	0.42
Folic acid	6	284	24.4 ± 8.5	665	20.3 ± 8.4	*< 0.001*	0.3 ± 44.8	− 3.5 ± 10.5	*< 0.001*
	12	89	27.5 ± 8.2	388	21.8 ± 9.1	*< 0.001*	8.0 ± 10.1	4.9 ± 8.8	0.10
	24	154	25.4 ± 9.4	184	21.3 ± 9.7	*0.001*	7.6 ± 12.3	4.5 ± 12.35	*0.020*
	36	103	24.2 ± 10.7	75	22.4 ± 9.9	0.27	7.1 ± 12.8	5.3 ± 11.4	0.33
	48	43	25.2 ± 10.0	17	19.3 ± 9.1	*0.041*	8.5 ± 11.6	2.5 ± 10.8	0.08
Vitamin B_{12}	6	284	324.0 ± 113.5	665	307.9 ± 108.5	0.065	17.8 ± 84.3	− 2.4 ± 101.5	*0.009*
	12	223	359.4 ± 111.6	544	339.6 ± 113.9	*< 0.001*	16.8 ± 84.0	− 1.5 ± 101.6	*< 0.001*
	24	202	386.5 ± 214.1	275	397.8 ± 217.5	0.65	88.7 ± 214.3	79.7 ± 238.4	0.74
	36	119	384.2 ± 258.2	134	384.9 ± 235.6	0.61	110. 6 ± 251.5	105.1 ± 269.9	0.90
	48	80	381.1 ± 227.7	53	363.0 ± 174.9	0.62	60.2 ± 176.7	78.7 ± 216.3	0.69
MMA	6	123	240.0 ± 178.2	291	203.6 ± 96.8	*0.008*	44.4 ± 142.3	31.2 ± 97.2	0.39
	12	81	245.4 ± 101.4	254	227.0 ± 112.5	0.19	43.4 ± 143.0	31.7 ± 97.2	0.50
	24	91	223.0 ± 108.2	114	215.5 ± 107.1	0.62	46.5 ± 140.1	31.3 ± 150.8	0.64
	36	47	227.5 ± 131.9	45	231.3 ± 137.1	0.89	− 12.6 ± 137.8	101..8 ± 169.9	0.07
	48	26	229.5 ± 123.4	13	268.9 ± 96.3	0.32	21.3 ± 95.0	146.0 ± 53.7	0.10

Hb, hemoglobin; *MCV*, mean corpuscular volume; *PTH*, parathyroid hormone; *MMA*, methyl malonic acid; *FU*, follow-up

number of deficiencies (one or more) was significantly lower for users at all time intervals.

Table 6 shows the outcomes of the binomial logistic regression model assessing the influence of multivitamin supplementation of serum levels postoperatively. This indicates a significant influence of multivitamin supplementation mainly on ferritin, folic acid, vitamin B_1, and hypervitaminosis vitamin B_6. The total amount of deficiencies was also independently significantly lower in users.

Discussion

This study shows that many vitamin deficiencies occur after SG, regardless of the non-malabsorptive nature of the SG procedure. This confirms that postoperative nutritional management after SG is highly underestimated. Endocrine Society Clinical Practice Guidelines recommend that long-term vitamin and mineral supplementation should be considered in all patients undergoing BS, with those who have had malabsorptive procedures requiring potentially more extensive replacement therapy to prevent nutritional deficiencies [23]. The recommendations in order to prevent a vitamin deficiency are mainly focused on the malabsorptive procedures. No recommendations are made for SG. In the American Society for Metabolic and Bariatric Surgery (ASMBS) guidelines 2008 [20], SG was not even included yet as a separate procedure in the postoperative vitamin supplementation section. However, SG is now mentioned in the updated statements dating from 2013 to 2016 [24, 25].

Vitamin B_{12} and Folic Acid

Vitamin B_{12} plays a vital role in DNA synthesis and in neurologic functioning [26]. A vitamin B_{12} deficiency can lead to macrocytic anemia, glossitis, fatigue, numbness and paresthesia in extremities, ataxia, changes in reflexes, demyelination and axonal degeneration with ultimately irreversible neuropathy, light-headedness or vertigo, tinnitus, and altered mental status [20, 27, 28]. Frequently, low levels of serum folic acid accompany vitamin B_{12} deficiency and they can cause hyperhomocysteinaemia, creating a risk factor for atherosclerosis [5].

Vitamin B_{12} is absorbed in the terminal ileum when bound to intrinsic factor (IF). The glycoprotein IF is produced in the parietal cells in the antrum of the stomach and in the duodenum. These parts are partially preserved after the SG. Therefore, vitamin B_{12} deficiencies are expected to be less common after SG. However, by resecting two thirds of the stomach, a considerable reduction in the number of parietal cells occurs, and less IF might be produced [5, 12, 13]. The folic acid absorption occurs mainly in the jejunum and remains well after SG [29]. Because vitamin B_{12} is a cofactor for the conversion of folic acid to its active form, low B_{12} might lead to folic acid deficiencies [30]. Prevalence of vitamin B_{12} deficiency at 2–5 years postoperatively is 4–20% after SG [19, 24]. In this study, the results were similar with

Table 5 Percentages of preoperative and de novo deficiencies. Baseline: users $N = 291$, non-users $N = 679$

Serum variables	User preoperative deficiency *N* (%)	Non-user preoperative deficiency *N* (%)	*P* value preoperative deficiency	Months of FU	*N* Users	User de novo deficiency *N* (%)	*N* Non-users	Non-user de novo deficiency *N* (%)	*P* value de novo deficiency
Hb	12 (4.3%)	30 (4.5%)	0.49	6	283	14 (5.1%)	664	33 (5.2%)	1.00
				12	223	15 (7.4%)	594	31 (5.7%)	0.40
				24	201	26 (20.3%)	616	22 (9.4%)	*0.005*
				36	120	12 (18.8%)	137	3 (2.9%)	*0.001*
				48	80	2 (5.4%)	53	1 (2.8%)	0.599
MCV micro macro	13 (4.5%) 1 (0.3%)	27 (4.0%) 5 (0.7%)	0.56	6	283	2 (0.7%)/0	664	3 (0.5%)/9 (1.4%)	0.13
				12	223	0/0	594	1 (0.2%)/8 (1.4%)	0.19
				24	201	3 (2.0%)/0	616	3 (1.2%)/2 (0.8%)	0.45
				36	120	2 (2.3%)/2 (2.3%)	137	0/0	0.06
				48	80	2 (6.5%)/0	53	1 (4.3%/)/0	1.00
Iron	124 (42.6%)	247 (36.4%)	0.040	6	284	19 (11.7%)	665	53 (12.5%)	0.89
				12	223	14 (12.2%	594	33 (9.6%)	0.48
				24	201	16 (22.5%)	616	11 (7.7%)	*0.004*
				36	120	7 (20%)	137	6 (8.6%)	0.12
				48	80	1 (5.6%)	53	1 (5.6%)	0.972
Ferritin	16 (5.7%)	28 (4.2%)	0.22	6	284	3 (1.1%)	665	20 (3.1%)	0.10
				12	223	8 (3.6%)	594	22 (3.8%)	1.00
				24	202	16 (8.1%)	275	35 (13.1%)	0.10
				36	120	11 (9.8%)	137	9 (7.6%)	0.56
				48	80	6 (8.5%)	53	7 (14.3%)	0.38
PTH	131 (45.0%)	301 (44.3%)	0.45	6	284	9 (5.8%)	665	18 (4.9%)	0.67
				12	223	10 (8.8)	594	25 (8.0%)	0.84
				24	201	32 (24.6%)	616	51 (24.8%)	1.00
				36	120	11 (19.3%)	137	12 (16.0%)	0.65
				48	80	9 (16.4)	53	7 (21.2%)	0.58
Calcium	0	0	–	6	284	0	665	0	–
				12	223	0	594	0	–
				24	201	0	616	1 (0.4%)	1.00
				36	120	0	137	0	–
				48	80	1 (1.3%)	53	0	1.00
Albumin	0	0	–	6	284	0	665	1 (0.2%)	1.00
				12	223	0	594	1 (0.2%)	1.00
				24	201	0	616	1 (0.2%)	1.00
				36	120	0	137	0	-
				48	80	0	53	0	-
Vitamin D	199 (68.4%)	491 (72.3%)	0.12	6	284	0	665	5 (2.7%)	0.18
				12	223	10 (2.9%)	594	34 (5.4%)	0.14
				24	202	11 (28.2%)	275	11 (20.4%)	0.46
				36	120	16 (24.2%)	135	13 (18.1%)	0.41
				48	80	2 (6.5%)	52	1 (6.7%)	1.00
Vitamin B_1	10 (3.4%)	27 (4.0%)	0.42	6	284	5 (1.8%)	665	27 (4.2%)	0.08
				12	223	1 (0.5%)	594	14 (2.6%)	0.08
				24	201	1 (0.7%)	275	14 (6.0%)	*0.012*
				36	119	1 (1.2%)	197	1 (1.0%)	0.82
				48	79	1 (1.9%)	52	0	1.00
Vitamin B_6 hypo	2 (0.7%)	7 (1.0%)	0.042	6	284	0/128 (45.4%)	665	5 (0.8%)	0.12

Table 5 (continued)

Serum variables	User preoperative deficiency *N* (%)	Non-user preoperative deficiency *N* (%)	*P* value preoperative deficiency	Months of FU	*N* Users	User de novo deficiency *N* (%)	*N* Non-users	Non-user de novo deficiency *N* (%)	*P* value de novo deficiency
hyper	43 (14.8%)	70 (10.3%)		12	221	0/112 (51.1%)	591	263 (39.9%)	*0.010*
				24	201	0/68(45%)	275	4 (0.7%)/234 (40.1%)	*0.022*
				36	119	2 (2.3%)/43 (48.9%)	134	2 (0.8%)/84 (32.2%)	0.09
				48	79	0/37 (66.1%)	52	1 (0.8%)/43 (35.5%) 1 (2.6%)/21 (53.8%)	0.06
Folic acid	32 (11.0%)	109 (16.1%)	0.024	6	284	4 (1.6%)	665	22 (4%)	0.09
				12	89	0	388	26 (4.6%)	*< 0.001*
				24	154	1 (0.5%)	184	22 (8.5%)	*< 0.001*
				36	103	5 (4.2%)	75	5 (4%)	1.000
				48	43	1 (1.3%)	17	1 (2.0%)	0.73
Vitamin B_{12}	51 (17.5%)	147 (21.6%)	0.08	6	284	18 (7.7%)	665	58 (11.1%)	0.15
				12	223	5 (3.0%)	544	31 (7.5%)	*0.045*
				24	202	9 (7.6%)	275	25 (14.5%)	0.09
				36	119	5 (7.5%)	134	6 (8.3%)	1.00
				48	80	4 (9.5%)	53	1 (5.6%)	1.00
MMA low elevated	91 (63.6%)	185 (73.1%)	0.12	6	123	69 (56.1%)/17 (13.8%)	291	185 (63.6%)/23 (7.9%)	0.14
	11 (7.7%)	18 (7.1%)		12	81	37 (45.7%)/17 (21.0%)	254	142 (55.9%)/39 (15.4%)	0.26
				24	91	55 (60.4%)/14 (15.4%)	114	66 (57.4%)/26 (12.6%)	0.33
				36	47	28(59.6%)/8(17.0%)	45	25(55.6%)/7 (15.6%)	0.87
				48	26	15 (57.7%)	13	4 (48.7%)	0.20
One or more deficiencies	200 (68.7%)	516 (76%)	*0.021*	6	284	20 (7.0%)	665	90 (13.5%)	*0.004*
				12	223	10 (4.5%)	591	63 (10.9%)	*0.006*
				24	201	23 (11.6%)	275	67 (24.6%)	*< 0.001*
				36	119	24 (20.3%)	134	24 (17.8%)	0.36
				48	79	12 (15.0%)	52	7 (13.2%)	1.00
Total patients with de novo deficiencies				6	284	20 (7.0%)	665	90 (13.5%)	*0.004*
				12	223	28 (12.6%)	591	129 (21.7%)	*0.003*
				24	201	36 (17.8%)	275	114 (41.5%)	*< 0.001*
				36	119	41 (34.2%)	134	63 (46.3%)	*0.001*
				48	79	12 (15%)	52	28 (52.8%)	*< 0.001*

Hb, hemoglobin; *MCV*, mean corpuscular volume; *PTH*, parathyroid hormone; *MMA*, methyl malonic acid; *FU*, follow-up

significantly less de novo deficiencies in de patients who used optimized vitamin supplementation.

For serum cobalamin < 200 pmol/L, it is unclear whether there is a functional cobalamin deficiency and cobalamin assays to diagnose a clinical deficiency that has a failure rate of 22–35% [27, 28, 31]. (MMA or homocysteine are useful in diagnosing patients who have cobalamin deficiency). The sensitivity of the available metabolic tests has facilitated the development of the concept of subclinical cobalamin deficiency [26, 28]. However, there is no clear policy about these additional parameters yet. MMA is recommended in the ASMBS. However, this parameter is not included in the Endocrine Society guidelines.

Prevalence of folic acid deficiencies is reported in up to 65% patients after bariatric surgery [19, 24]. Regardless of the preparation, multivitamin supplements providing 400 μg/g folic acid can effectively prevent the development of folic acid deficiency after RYGB. This suggests that the

Table 6 Binomial logistic regression model assessing the influence of multivitamin supplementation of serum levels postoperatively

	Coefficient	Standard error	Significance
After 6 months			
Ferritin	− 0.004	0.002	*0.035*
Folic acid	− 0.058	0.25	*0.020*
Vitamin B_1	− 0.016	0.007	*0.017*
After 12 months			
Folic acid	− 0.066	0.015	*< 0.001*
After 24 months			
Folic acid	− 0.128	0.047	*0.007*
Hypervitaminosis vitamin B_6	− 0.036	0.014	*0.012*
Vitamin D	0.040	0.018	*0.027*
One or more deficiencies			*0.039*

intake of folic acid from the diet and routine multivitamins is generally sufficient to prevent folic acid deficiency [21]. This study showed 0–8.5% of folic acid deficiencies, with significantly less de novo deficiencies in the user group. The binomial logistic regression model also showed a significant influence of multivitamin supplementation on serum folic acid levels.

Iron, Ferritin, Hemoglobin, and MCV

The absorption of iron can occur throughout the small intestine; it is most efficient in duodenum and proximal jejunum, which remain intact after SG. However, a decreased hydrochloric acid production in the stomach after resecting the fundus during SG procedure can affect the reduction of iron from the ferric (Fe^{3+}) to the absorbable ferrous state (Fe^{2+}) [21]. The use of proton pump inhibitors can also affect the production of hydrochloric acid [20].

The prevalence of iron deficiency in 3to 10 years postoperatively is reported to occur in < 18% after SG [20]. The risk for iron deficiency increases over time, with some series reporting that more than half of the subjects had low ferritin levels 4 years after RYGB. Serum iron levels alone are a poor marker for iron deficiency. Serum ferritin is more specific and is the preferred measurement worldwide, although it is better to combine it with total transferrin saturation [5].

In this study, low ferritin levels were found in 6% of patients in the user group and 4% in non-user group before surgery and in 1–14%, postoperatively. Subsequently, anemia was found in 4% of patients in both groups preoperatively and in the postoperative period in up to 20%. Although not an adequate marker for deficiencies, serum iron concentrations did show significant differences between the two groups at 2 years in favor of regular multivitamin use (Table 5). Based on an inventory from a different ongoing randomized study (VITAAL I study), iron concentrations of the customized WLS supplement was increased from 21 mg (150% RDI) to 28 mg (200% RDI) in December 2017. Patients included in this study did not use this new supplement. However, the results from this study confirm the need for this iron adjustment in the WLS supplement.

Calcium, Vitamin D, and PTH

Calcium is absorbed preferentially in the duodenum and proximal jejunum, and its absorption is facilitated by vitamin D in an acid environment. Vitamin D is absorbed preferentially in the jejunum and ileum. Vitamin D has a key role in calcium balance and bone structure. Classical actions of vitamin D include intestinal calcium absorption by aiding the active transport of this ion through the enterocytes, bone resorption, and calcium reabsorption at the distal renal tubules in the presence of parathyroid hormone (PTH).

A vitamin D deficiency is a common phenomenon before and after bariatric surgery. The reported prevalence of vitamin D deficiency prior to surgery ranges between 54 and 80% [32]. The reported prevalence of vitamin D deficiency have been attributed to inadequate intake, a lifestyle of limited sun exposure, and decreased bioavailability of vitamin D due to sequestration of the fat-soluble vitamin in the excess adipose tissue [32]. Secondary hyperparathyroidism may be a contributory factor resulting in increased 25 (OH) D hydroxylation, therefore decreasing vitamin D levels. In addition to the classically described hyperparathyroidism, several cases of osteomalacia have been reported following malabsorptive weight loss surgeries [33, 34]. In this study, vitamin D deficiencies were in 70% of the patients preoperatively, with a drastic decline (probably due to aggressive supplementation) to 0.5–7.0% in the first 5 years after sleeve gastrectomy. De novo deficiencies for vitamin D were totally low because of the large amount of preoperative deficiencies. This most obviously led to underpowering and finding any significance percentage wise.

Vitamin B_1

Although rare, Beriberi is caused by a thiamin deficiency that can affect various organ systems, including the heart, gastrointestinal tract, and peripheral and central nervous systems. Early detection and prompt treatment of thiamin deficits in these individuals can help to prevent serious health consequences. Most deficiencies do not lead to any clinical symptoms, but when beriberi develops and is misdiagnosed for even a short period, irreversible neuromuscular disorders, permanent defects in learning, and short-term memory might develop as well as coma, and even death [21]. Thiamine is absorbed in the proximal jejunum by an active transport system and is abundantly available from all sorts of foods.

Vomiting and inadequate responses by patient and healthcare professional are thus probably the main reasons for developing beriberi and explain the higher prevalence in the first postoperative months.

Prevalence of thiamine deficiency after bariatric surgery ranges from < 1 to 49% and varies by type of surgery and postoperative time frame [19, 24]. Risk of thiamine deficiency increases with vomiting and excessive alcohol use [19, 24]. Low levels of vitamin B_1 were present in 5.5% 1 year after SG in the study by Van Rutte and colleagues [5]. In this study, vitamin B_1 deficiencies were seen in 3.6% preoperatively and postoperatively, varying between 0.5% after 6 months and to 6% after 2 years. The specialized multivitamins seem to almost hold the right amount of thiamin with 2 mg, while no clinical symptoms developed and significantly reduced the amount of low serum vitamin B_1 levels. A calculated 2.75 mg should theoretically be sufficient in compliant and non-vomiting patients.

Vitamin B_6

Excessive hypervitaminoses B_6 can cause neurologic symptoms. The number of patients with hypervitaminosis B_6 had doubled 1 year after surgery in the study by Van Rutte et al. [5], which might be the effect of multivitamin supplementation. In this study, similar results were seen until 3 years after surgery. Similar results were found in the study by Punchai et al. [35]. In general, a dose of 2 mg is more than sufficient to prevent deficiencies and even lead to a decrease of 50% hypervitaminosis cases. A dose of 1.5 mg daily should prevent any deficiencies without increasing the amount of hypervitaminosis too much. Problems may arise when non-bariatric specialists prescribe vitamin supplementation. In the case report by Cupa et al. [36], a severe case of hypervitaminosis B6 was described, which was caused by a supplementation of 300 mg of vitamin B_6 per day for the last 6 months.

Strengths and Limitations

Major strengths of this study were the large population and the follow-up of 4 years postoperatively. Besides that, the classification of users and non-users was objectively confirmed by available MVM usage data. In the non-WLS group, no distinction is made between patients who use the regular MVS or say they do, but actually do not use any MVS which possibly causes publication bias. Limitations of this study were the retrospective character and the loss of follow-up. However, several factors are difficult to account for in a large study like this, e.g., compliance, protocol changes, changes in WLS supplement composition, and social economic status.

In terms of compliance, the WLS user group consists of 279 patients (29.0%) and the non-WLS-user group consists of 671 patients (71%) at the beginning of this study. The information of the compliance of intake of other vitamins than WLS Optimum is subjectively by only asking the patients themselves. Therefore, it is unclear how many patients reported use, but in practice did not use, of any MVS, which possibly influences the outcomes. The study by Navarro et al. reported a serum folic acid concentration of fivefold compared with baseline after oral intake of standard MVS (containing 1.6 mg folic acid) [37]. However, this study was performed in healthy adults without obesity, comorbidities, and bariatric surgery. Therefore, folic acid could be used as a marker for compliance, but it is unclear whether this also applies to the bariatric surgery target group. Besides that, information of the compliance of intake of all MVS is not collected consistently in all the included study patients. Additionally, lifelong compliance with a daily MVS seems challenging for patients.

Over the course of time, the composition of the WLS supplement has changed. Customized WLS supplement has adjusted the concentrations of iron (from 150 to 200% RDI), vitamin B_{12} (from 400 to 4000% RDI), vitamin D (from 150 to 1500% RDI), and folic acid (from 150 to 250% RDI) in December 2017. These new supplements were not used in this study, but theoretically reduce the amount of deficiencies even further.

Probably, due to underpowering, a number of mean serum concentrations showed no significant differences between the two groups at all FU moments. Mean vitamin B_{12} concentrations showed only a significant difference 1 year postoperatively in favor of the WLS-user group. Mean serum vitamin D concentrations showed a significant difference at 1 and 2 years postoperatively in favor of the WLS-user group. However, all patients use an additional vitamin D supplement besides the WLS supplement or regular MVS. Therefore, it is difficult to assess the differences in serum vitamin D in both groups. Our patients used the previous WLS version whose composition is described in Table 1 but the new version might make adding colecalciferol unnecessary. However, these results confirm once again the need for this adjustment of the WLS supplement. The average same amounts as supplemented in these patients (75 μg) are now in the current version of WLS. The results did however show that the total number of de novo deficiencies was significantly reduced by the use of the new supplement throughout the study period.

Finally, education, occupational status, and income are the most widely used indicators of socioeconomic status (SES). Each of these measures can capture distinctive aspects of social position but they are not interchangeable, nor are the immune to interactions with such variables as race/ethnicity and gender. There is considerable evidence demonstrating that an individual's educational status is an important predictor of mortality and morbidity. Persons in the lower strata have been found to have lower life expectancy and higher mortality rates from all causes of death combined, and higher rates of several major mental disorders [38]. Social class is clearly an important variable in studies of health and is frequently included in epidemiologic studies. No correction has been made for SES in this study, which may cause publication bias. However, it is well-known that poor measurement of social class leading to random misclassification will dilute any actual bivariate associations. If the wrong indicator of social class is used, publication bias through misleading results may be obtained [38]. SES can also involve the choice of using MVS. The patients themselves paid MVS. However, the WLS Optimum is much more expensive than over-the-counter MVS.

Conclusion

Vitamin deficiencies are very common, and postoperative nutritional management after SG is highly underestimated. The use of the specialized WLS supplement resulted in higher mean serum concentrations of ferritin, folic acid, vitamin B_1, and vitamin D and deficiencies in vitamin B_{12}, ferritin, folic acid, vitamin B_1, and vitamin B_6. The study showed that SG patients could not just only use lifelong standard MVM but could also benefit even more from the specialized supplements.

Compliance with Ethical Standards

The study protocol was approved by the National Medical Ethics Review Committee of the Radboud University Medical Center (protocol number 2017-3412) and Local Ethical Committee of the CZE (protocol number nWMO2017-45), and was conducted in concordance with the principles of the Declaration of Helsinki.

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

Ethical Approval Statement For this type of study, formal consent is not required.

Informed Consent Statement Does not apply

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